

# Pericardial involvement as an initial presentation of anaplastic large cell lymphoma

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Anaplastic large cell lymphoma (ALCL) is a CD30-positive neoplasm of either T-cell or null-cell lineage accounting for 2% to 8% of all lymphomas.<sup>1</sup> Most frequently, patients with ALCL present with advanced disease with extranodal involvement.<sup>2</sup> The central nervous system (CNS) (30%), gastrointestinal tract (25%), and bone marrow are the most commonly involved extranodal sites.<sup>3</sup> Cases of ALCL with a primary cardiac mass have been previously reported.<sup>3-5</sup> However, ALCL with pericardial involvement and without an associated cardiac mass has not been reported. This case illustrates the importance of considering ALCL in the differential diagnosis on initial presentation of a young patient with unexplained pericardial effusion.

## Case

A 22-year-old man with no previous cardiac disease history was admitted to our institution for new-onset cardiomegaly noted on a chest x-ray scan at an urgent care centre. He had developed progressive dyspnea and worsening cough for 10 days before admission and had a 4.5-kg weight loss during a 1-week period. His medical history was relevant for infectious mononucleosis (IM) diagnosed 4 years previously. On presentation, the patient was dyspneic and tachycardic, with a temperature of 37.3°C, an oxygen saturation of 94% on room air, a blood pressure of 116/79 mm Hg, and a paradoxical pulse of 15 mm Hg. A physical examination was notable for jugular venous distention, palpable nontender lymphadenopathy in the right and left axillary and right posterior cervical chain, clear lungs, and muffled heart sounds. His hemogram results, serum chemistry results, hepatic enzyme levels, and inflammatory marker levels were normal except for a slight elevation in erythrocyte sedimentation rate (35 mm/h). The patient's test results were negative for HIV by immunoassay and his lactate dehydrogenase level was normal. His viral titre results were positive for Epstein-Barr virus (EBV) viral capsid antigen-immunoglobulin (Ig) G and negative for EBV viral capsid antigen-IgM, EBV nuclear antigen, and cytomegalovirus IgG antibody. A standard 12-lead electrocardiogram showed sinus tachycardia at 120 beats/min with nonspecific ST-T wave changes. An initial 2-dimensional transthoracic echocardiogram (TTE) showed a 5-cm circumferential pericardial effusion with diastolic collapse of the left and right atria. Doppler inflow tract velocity across the mitral valve revealed exaggerated respiratory phasic changes consistent with cardiac tamponade physiology.

Pericardiocentesis yielded 2000 mL of fluid, from which bacterial, fungal, and acid-fast bacillus cultures grew no organisms. A cell count showed 80% of the cells to be lymphocytes. Acute and convalescent viral serologic tests had negative results. Cytologic examinations of the pericardial fluid showed reactive mesothelial cells and neoplastic cells (Figure 1). Immunohistochemical stains of the pericardial fluid demonstrated coexpression of the neoplastic cells to CD30-anaplastic lymphoma kinase 1 (ALK-1), epithelial membrane antigen, and

## EDITOR'S KEY POINTS

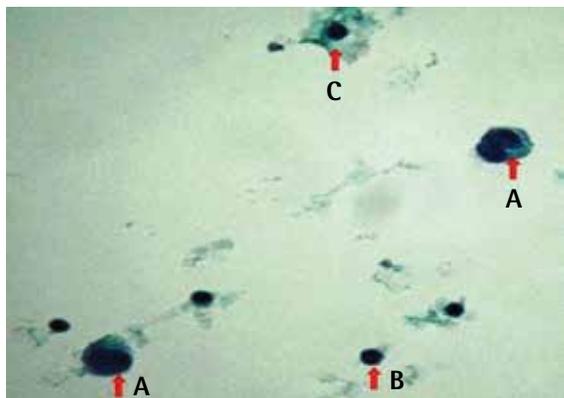
- Associations between lymphoma and the heart are underestimated. Cardiac anaplastic large cell lymphoma (ALCL) is usually diagnosed during autopsy; therefore, high clinical suspicion is warranted to detect involvement promptly.
- Medical practitioners should familiarize themselves with the role of pericardial fluid cytology and transthoracic echocardiography in diagnosing cardiac ALCL. Knowledge of various presentations of lymphoma is essential for day-to-day practice.
- This case highlights a valuable approach when encountering ALCL and documents the rare occurrence of isolated pericardial effusion on presentation. Always consider malignancy in young patients who present with pericardial effusion in the absence of uremia.

## POINTS DE REPÈRE DU RÉDACTEUR

- On sous-estime les associations entre les lymphomes et le cœur. Le lymphome cardiaque anaplasique à grandes cellules (LAGC) est habituellement diagnostiqué à l'autopsie; par conséquent, il faut une forte suspicion clinique pour détecter sans délai un tel lien.
- Les médecins devraient se familiariser avec le rôle de la cytologie du liquide péricardique et de l'échocardiographie transthoracique dans le diagnostic d'un LAGC cardiaque. Il est essentiel, dans la pratique au quotidien, de connaître les diverses présentations des lymphomes.
- Ce cas met en évidence une approche utile en présence d'un LAGC et documente la rare occurrence d'un épanchement péricardique isolé lors de sa présentation. Il y a lieu de toujours envisager un cancer chez de jeunes patients qui présentent un épanchement péricardique en l'absence d'urémie.

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**Figure 1. Pericardial fluid cytology (Papanicolaou stain):** A) 2 malignant lymphoma cells with large folded pleomorphic nuclei and prominent nucleoli. B) Cytologically mature lymphocytes. C) Cytologically mature histiocytes. Magnification of a 396 × 207–mm (96 × 96 DPI) area.



DPI—dots per inch.

vimentin with weak CD45 expression. Histopathology of the subclavicular lymph nodes revealed diffuse atypical lymphoid infiltrates with characteristic lymphoma cells (**Figure 2**). Immunohistochemical studies of the lymph nodes revealed that the malignant cells stained positively for markers identical to those in the pericardial fluid. A Ki-67 immunostain labeled 90% of the neoplastic cells, indicating a high mitotic rate consistent with aggressive lymphoma. Results of a bone marrow biopsy analysis by flow cytometry were negative for lymphoma. Cerebrospinal fluid analysis results were negative for lymphoma cells. Further staging by computed tomography scans showed bilateral pleural effusions, and adenopathy of the left axilla, mediastinum, hilum, and retroperitoneum.

Overall findings indicated stage IV-B primary systemic ALK-1–positive ALCL with pericardial involvement. A repeat TTE on hospital day 4 showed no evidence of tamponade or intracardiac mass. Given his young age, advanced presentation, and 2% to 5% future risk of CNS disease,<sup>6</sup> the patient was started on a hyperfractionated CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen with an alternating dose of methotrexate and cytarabine every 3 to 4 weeks for 6 cycles.<sup>7,8</sup> A follow-up whole-body positron emission tomography scan done at month 14 showed complete disease remission.

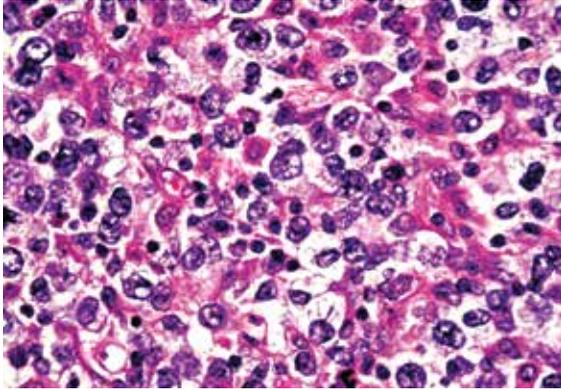
## Discussion

Cardiac involvement from lymphomas can be primary or secondary. Primary cardiac lymphoma exclusively

involves the heart or pericardium and constitutes a rare entity, accounting for less than 1% of all extranodal lymphomas.<sup>4</sup> In contrast, tumours showing other sites of involvement, such as mediastinal lymphadenopathy or disease below the diaphragm, most likely represent secondary lymphomatous involvement of the heart. In some autopsy series, secondary heart involvement by lymphoma was identified in 10% to 30% of the cases.<sup>4</sup> Lymphomas have been reported to constitute more than 9% of the total metastases to the heart, and up to 20% of patients with lymphoma are found, at autopsy, to have cardiac involvement.<sup>9</sup> Anaplastic large cell lymphoma has rarely been found to involve the heart, even in large case series of the disease.<sup>10</sup> Primary effusion lymphoma, another rare neoplasm, occurs in HIV patients in association with malignant peritoneal, pericardial, or pleural effusions, usually in the absence of a tumour mass and with rare lymph node involvement.<sup>11,12</sup> Although this patient had nodal involvement, his HIV immunoassay results were negative and consequently primary effusion lymphoma was excluded. Modes of cardiac or pericardial involvement from malignant lymphoma include retrograde lymphatic spread, hematogenous spread, and direct extension from other intrathoracic tumour masses.<sup>9</sup> Thus,

**Figure 2.** A section of subclavicular lymph node (hematoxylin and eosin stain) showing population of sheets of anaplastic lymphoma cells with irregular, eccentric, horseshoe-shaped nuclei and prominent nucleoli identical to those shown in Figure 1:

*Magnification of a 127 × 95-mm (300 × 300 DPI) area.*



DPI—dots per inch.

heart involvement in non-Hodgkin lymphoma is usually a late manifestation of disseminated disease.

Early detection of cardiac involvement is crucial to selecting appropriate treatment. Transthoracic echocardiography is an excellent initial imaging tool that visualizes pericardial effusion easily and also reveals the presence of any intracardiac mass. In the scenario of a questionable intracardiac mass on TTE, accurate diagnosis with 100% sensitivity can be achieved with transesophageal echocardiography.<sup>5,13</sup> Cytologic analysis of the pericardial fluid does not always lead to a definitive diagnosis because the effusion might be reactive (as opposed to containing neoplastic cells), resulting in a sensitivity as low as 67% even for a diagnosis of primary cardiac lymphoma.<sup>5</sup> However, a high index of clinical suspicion must be maintained if 1 or more diagnostic studies are inconsistent.

Prompt combination chemotherapy, with or without adjuvant radiotherapy, remains the mainstay of treatment of cardiac lymphoma.<sup>14,15</sup> Most investigators reported that 60% to 90% of ALCL cases responded well to chemotherapy.<sup>16-18</sup> Further, several studies have identified that patients with ALK-1-positive ALCL have a 5-year overall survival rate ranging between 70% and 93%.<sup>19-21</sup> Also, in pediatric populations with ALCL that presented initially without CNS disease, relapse of ALCL with CNS disease was very rare.<sup>22</sup> However, rates of relapse of ALCL with CNS disease in the adult population without initial CNS disease are still unclear. With aggressive chemotherapy, our patient showed no recurrence of effusion or subsequent cardiac or CNS involvement.

Several points of interest are illustrated by this case. First, malignancy should be ruled out whenever a young patient presents with pericardial effusion. Second, this case showed no bone marrow involvement of ALCL, which was described as a rare event by Chan et al.<sup>23</sup> Third, the possibility that a history of IM predisposed the patient to ALCL cannot be excluded. A pooled analysis of data from 17 case-control studies showed that self-reported history of IM was associated with an increased risk of non-Hodgkin lymphoma.<sup>24</sup> Although the causative role of EBV cannot be explained, EBV infectivity has been seen in immunocompromised patients with ALCL. At least 64 cases of ALCL have demonstrated evidence of EBV positivity.<sup>25</sup> Of interest, our patient developed antibodies to EBV; unfortunately, for clinical reasons, *in situ* hybridization studies for EBV-encoded RNA could not be performed on the pericardial aspirates. Finally, Ki-1 antigen expression is associated with relatively favourable outcomes among lymphomas of similar histologic subtypes.<sup>17</sup> In summary, this young patient with early detection of pericardial involvement and Ki-1 antigen expression had a good outcome with hyperfractionated CVAD therapy during a follow-up period of 14 months.

### Conclusion

Although very rare, ALCL should be considered in the

differential diagnoses of unexplained pericardial effusion in young patients. Early detection of heart involvement in ALCL with appropriate diagnostic procedures is crucial for favourable outcomes.

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#### Competing interests

None declared

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