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CASE REPORT

Treatment challenges and outcome of Intra-cardiac Lymphoma in a resource-limited setting: A case report

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Summary

Malignant lymphoma, presenting as primary intra-cardiac mass, is rare in children. Without timely intervention, morbidity and mortality may be high in this condition, particularly when it is associated with pericardial effusion and cardiac tamponade.

A case of a 9-year old Nigerian girl with primary cardiac lymphoma associated with pericardial effusion and cardiac tamponade is reported. For reasons of parental financial incapability, the girl received only two of the six recommended courses of systemic chemotherapy following emergency pericardiostomy. She was alive and well for one year but suddenly died at home following the re-emergence of symptoms similar to the initial presentation of the primary neoplastic disease.

The response of primary cardiac lymphoma to combination chemotherapy alone is known to be good, thus, it is advocated as the treatment of choice for primary cardiac lymphoma where the resources for cancer treatment are limited and the cost of care is prohibitive. The lack of access to adequate chemotherapy may be the key factor responsible for the poor prognosis and fatality in this case.

Key words: *Chemotherapy; Health financing, Intra-cardiac lymphoma, Resource-limited setting, Nigeria.*

Introduction

Malignant Lymphomas (ML) are heterogeneous solid tumours of lymph nodes and lymphoid tissues. [1] Non-Hodgkin lymphoma (NHL), which is a subset of ML, accounts for over 60% of all childhood solid tumours in Nigeria. [1] Intra-cardiac mass is a rare initial presentation of ML and may lead to unexplained death, if undiagnosed. [2, 3] The right chamber of the heart, especially the right atrium is mostly involved in Primary Cardiac Lymphoma (PCL). The symptoms of PCL include cough, dyspnoea, orthopnoea, chest pain and fatigue. [2-6] Without timely intervention, mortality may be high in PCL, particularly if it is associated with pericardial effusion and cardiac tamponade. The case of a Nigerian girl with intra-cardiac lymphoma of the right atrium presenting with massive pleural effusion and cardiac tamponade is presented in this report. To our knowledge, this is the first reported case of PCL in Nigeria. This report is meant to highlight the challenges encountered in managing childhood cancers in a resource-limited setting. This is important when considered in the context of health financing which demands out-of-pocket payments from families seeking care.

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Case Description

O. R, a 9-year old Nigerian girl, presented at the Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun State, Nigeria, with dry cough and facial puffiness of one week duration and difficulty with breathing of one day duration. The illness was not associated with fever, weight loss, pedal swelling or urinary symptoms. She had been on

some water-based herbal concoction (constituents not known) for 5 days prior to presentation but with no improvement in the symptoms. She was the third of four children of parents who were peasant farmers. On physical examination, she was acutely ill-looking, dyspnoeic with facial puffiness and distended neck veins. There was no cyanosis and no significant peripheral lymph node enlargement. The body temperature, respiratory rate, heart rate, systolic blood pressure and SPO_2 were 36.7°C, 45 cycles/minute, 120 beats/minutes, 100mmHg and 97% respectively. The diastolic blood pressure was unrecordable. The pulse was of small volume and irregular. Other cardiovascular findings included precordial bulge, diffuse apex beat, distant heart sounds and pericardial rub. There were bi-basal crepitations in the lung fields and a small, firm, freely mobile mass in the para-umbilical region of the abdomen. There were no abnormalities in other systems.

Trans-thoracic Echocardiography (TTE) confirmed massive pericardial effusion with a huge mass attached to the anterior tricuspid valve that impeded diastolic flow into the right ventricle, a dilated right atrium with inter-atrial shift to the left almost collapsing the left atrial wall . Due to the urgency in the clinical situation, a complete cardiac function profile, including ejection fraction and fractional shortening, could not be done at the point of admission. A diagnosis of intra-cardiac mass with pericardial effusion and cardiac tamponade was made.

The girl was admitted for intensive care management and subsequently had emergency sub-xiphoid pericardiostomy (with 250ml of straw-coloured pericardial fluid effluent) and pericardial biopsy. Both the pericardial biopsy and cytology from pericardial effusion confirmed the diagnosis of B-Cell Non- Hodgkin Lymphoma, positive for CD 45 and CD 20 and negative for CD 3, CD30 and CD 34 on immunohistochemistry (Figures 1a-c).

Abdominal ultrasonography (USG) suggested a solid mass with a well-defined margin measuring 16.4cm x 9.7cm (L x AP) in the abdominopelvic region. Except for slight elevation in serum uric acid, serum lactate dehydrogenase (LDH) and erythrocyte sedimentation rate, all other investigations (peripheral blood film, cerebrospinal fluid analysis, bone marrow aspiration, serology, full blood counts, and serum chemistry) were essentially normal.

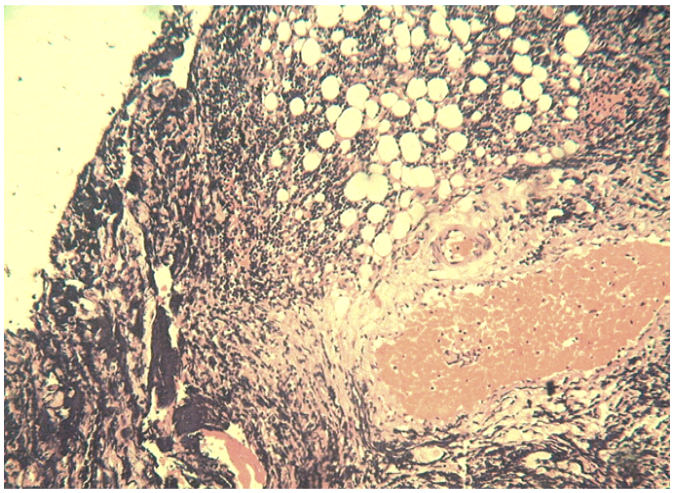

Figure1a. Photomicrongraph of the pericardial biopsy showing section of fibrofatty tissue consistent with the pericardium. There are loose sheets of monotonous malignant lymphoid cells infiltrating, destroying and replacing adipocytes. Infiltration and destruction of muscle and the foci of extensive necrosis are also obvious (H &E).

A combination chemotherapy consisting of cyclophosphamide, prednisolone, vincristine and cytosine arabinoside (COAP) with central nervous system (CNS) prophylaxis was administered in phases. The phases were preceded by a low dose cyclophosphamide, prednisolone and vincristine (COP) pre-phase therapy which lasted for one week and was meant to reduce the tumour load and avoid the risk of tumour lysis syndrome and cardiac rupture. The girl had significant clinical improvement following pericardiostomy and COP pre-phase chemotherapy. Thereafter, she was commenced on full COAP regimen but only received two out of the six scheduled courses of chemotherapy mainly due to parental financial constraints.

Nevertheless, the chemotherapy sessions were well tolerated with no derangement in the haematologic and biochemical parameters. Indeed, the serum uric acid and LDH levels became normal. Serial follow-up TTE at the end of COP pre-phase and at the end of each cycle of COAP confirmed significant reduction in intra-cardiac mass with normal cardiac funtions - ejection fraction of 48% and fractional shortening of 23% (Figures 2 and 3).

Abdominal USG also showed a complete resolution of the abdominal mass at the completion of the second chemotherapy course. The girl was on routine out-patient follow-up care and she was also monitored at home through telephone conversation whenever she missed her clinic appointments. She was alive and reported to be well for one year after the initial chemotherapy. She later reportedly became symptomatic with cough and breathlessness at home but the parents could not bring her to the hospital due to financial constraints. The girl reportedly died at home, two days into the illness.

Discussion

ML rarely presents initially as a primary intra-cardiac mass in immunocompetent individuals. [2-7] The incidence of ML is about 1.3% of all primary cardiac tumours and 0.5% of extra-nodal lymphomas, mostly among adults. [8] Similarly, this tumour is very rare among children. [2,5,6] The involvement of the heart in lymphoma can be primary or secondary. Primary cardiac involvement was first described pathologically as a separate entity in 1978; it was described as an extra-nodal lymphoma involving only the heart and/or pericardium. [8] Many other criteria have been included overtime in order to broaden the definition of PCL. [5,8] Currently, the generally accepted definition of primary cardiac lymphoma (PCL) is, any lymphoma presenting with clinical manifestations of cardiac disease especially if the bulk of the tumour is within the heart or pericardium. [4-6,8] However, the extent and /or the cut-offs for extra-cardiac involvement in PCL are yet to be defined. As such, a lot of extensive extra-cardiac involvements have been reported as PCL. [4, 5,

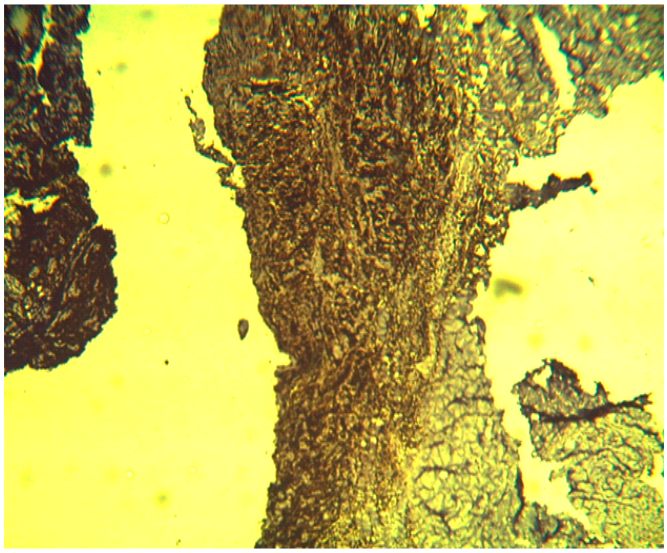

Figure 1b: Immunohistochemical staining positive for CD45

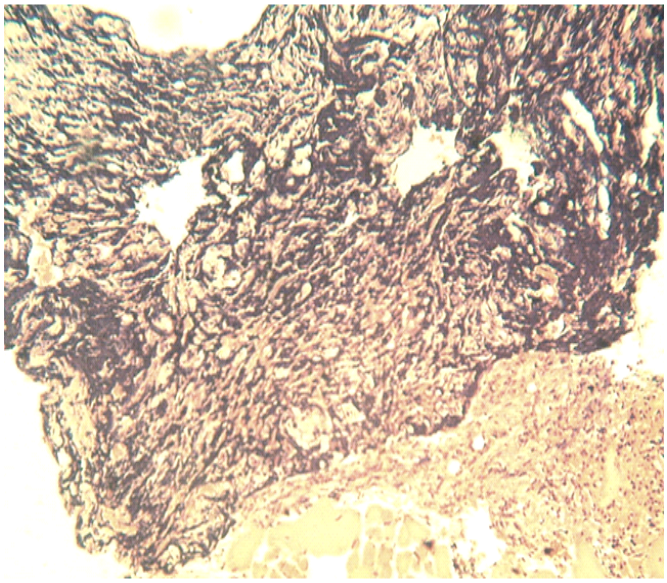

Figure 1c: Immunohistochemical staining positive for Cd20

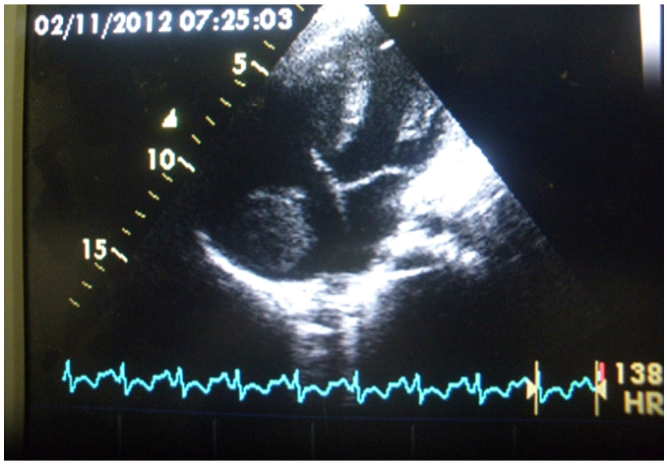

Figure 2: Trans-thoracic Echocardiography (TTE) at the completion of COP pre-phase

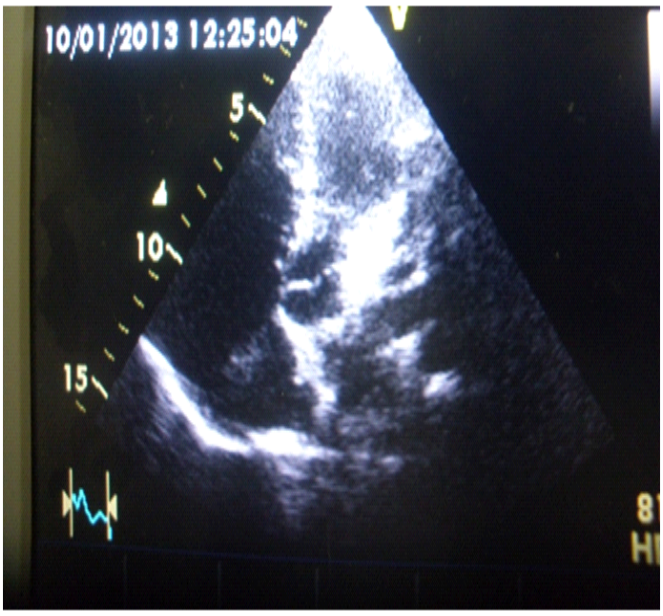

Figure 3: Trans-thoracic Echocardiography (TTE) at the completion of first cycle COAP

[8-10] However, reviews of reported cases suggested that bone marrow involvement in PCL is not common. [2,5-7] Previous reports revealed that the right chambers of the heart, especially the right atrium are the commonest site(s) affected with or without pericardial effusion in PCL. [5,6] In the index case, bone marrow studies were normal, the right atrium and tricuspid valves were involved and the child also developed pericardial effusion. Therefore, the index case fitted the definition of PCL.

The clinical manifestation of PCL is protean. Features include unresponsive heart failure, chest pain, pericarditis, arrythmias, pericardial tamponade, myocardial infarction and other constitutional symptoms as well as sudden death. [2-6,11-14] The fact that there is no pathognomonic symptom for this rare disease makes its diagnosis very challenging. In addition, delay in diagnosis/ treatment may adversely influence the outcome of the disease. Imaging techniques that have been reported to be useful in PCL include echo-cardiography, computerised tomograghic scan (CT) and magnetic resonance imaging (MRI). [2-6] TTE has a sensitivity of about 73% at detecting myocardial and intra-cavitatory lesions and pericardial effusion whereas the sensitivity of trans-oesophageal echocardiography (TEE) is close to100%. [4, 6] Either TTE or TEE should be carried out early whenever cardiac tumour is suspected or a patient presents with cardiac tamponade. In the index case, TTE confirmed massive pericardial effusion with a huge mass attached to the anterior tricuspid valve which impeded diastolic flow into the right ventricle, and a dilated right atrium with inter-atrial shift to the left almost collapsing the left atrial wall. Based on previous reports in the literature, no X-ray and/or electrocardiographic features are specific for PCL when performed as the first line non-invasive investigations. [5-7, 15] Unfortunately, Chest CT and MRI were not done in the index case for lack of funds.

The hallmark of diagnosis of PCL is usually cytologic evaluation of pericardial fluid or histologic evaluation of cardiac tissue. Previous studies involving large populations of non-Hodgkin lymphoma (NHL) cases have shown that lymphoma cells can be detected in serous fluid in up to 88% of cases while histopathological examination of biopsies of cardiac tissue confirmed diagnosis of PCL in 100% of cases. [5,16] B-cell NHL has been documented to be the most common type of PCL while diffuse large B-cell (DLBC) is the most frequent sub-type. [2-6,14]

The index case had sub-xiphoid pericardiostomy with pericardial biopsy as an emergency palliative treatment. Both histologic and cytologic studies confirmed NHL in the index case. Further description of the NHL subtype required immunohistochemistry on the tissue biopsy samples with positivity for CD 45 and CD 20 but negative for CD 3, CD30 and CD 34. CD 45 is a leucocyte common antigen (LCA) expressed by all haematopoetic cells and CD 20 is a pan B-cell marker. CD 3, CD 30 and CD 34 are markers of T-cells, Hodgkin disease and stem cells respectively. With this immunohistochemistry results, the diagnosis of B-cell NHL was confimed in the index child .

Different treatment modalities, including orthotopic heart transplantation, have been proposed for PCL. [5, 6, 17] Early systemic

chemotherapy is regarded as the most widely used treatment modality with a chance of cure. Radiotherapy or surgery, as a single treatment modality or in combination with chemotherapy, has no added advantage in terms of response to treatment, survival or relapse. [5, 6] Except for primary CNS lymphoma, outcome of treatment of PCL with chemotherapy alone is similar to that of other primary etxra-cardiac lymphomas that were treated with chemotherapy alone. [6] In some reports, the median time to relapse was 7 months with no reported case of relapse beyond 12 months when treated with chemotherapy alone. [5, 6] This compares favourably with the previous report on etxra-cardiac lymphomas from our centre. [18]

In the index case, the child's response to two cycles of COAP chemotherapy alone, with significant reduction in intra-cardiac mass and preserved cardiac function was remarkable. That the patient was alive and well for 12 months with this part-treatment supports previous reports that response to combination chemotherapy alone is favourable for the treatment of PCL. We advocate this as the treatment of choice in settings like ours where resources for cancer treatment and open cardiac surgery are limited. Early diagnosis and treatment is imperative and emergency pericardiocentesis is advised for associated pericardial tamponade. This should impact positively on the treatment outcome. Though diagnosed correctly and with good response to early intervention, the key challenge in this case was the fact that child did not complete the courses of chemotherapy due to financial handicap.

Conclusion

The essence of this report is to highlight the financial challenges encountered by many children with cancers in resource-limited parts of the developing world. The cost of anti-cancer drugs and treatment in general, are enormous and challenging in resource limited settings. It is, probably, the single most important factor responsible for the poor outcome in PCL in the index case. Therefore, it is attractive to recommend a health insurance scheme which is expanded to involve self-employed individuals and make special provisions for the care of children with cancers.

Authors' contributions: AO conceived the research idea. AO, OUU, AOO and DMA participated in the clinical management of the index case while KAO performed the histological examinations of all the biopsy samples. AO drafted the manuscript while AOO and DMA undertook the revision of the manuscript for sound intellectual contents. All the authors approved the final version.
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