LUPINE PUBLISHERS

ISSN: 2643-6760

Surgery & Case Studies: Open Access Journal

DOI: 10.32474/SCSOAJ.2021.06.000241

Case Report

Acute Appendicitis Concurrent with Cardiac Anaplastic Large Cell Lymphoma

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Received: July 5, 2021 **Published:** July 13, 2021

Abstract

Background: Anaplastic large cell lymphoma is a lymphoid neoplasm that develops from T cells or natural killer cells. It comprises approximately two percent of all Non-Hodgkin lymphomas and accounts for 16 percent of T cell lymphomas. Anaplastic large cell lymphoma can occur as a primary systemic variant, which presents as an extracutaneous disease. Common extranodal sites of involvement are bone, stomach, lung, liver, and skin. However, little is known regarding cardiovascular involvement of systemic anaplastic large cell lymphoma. As this case depicts, it is vital for surgeons to be aware of the complex properties of anaplastic large cell lymphoma involving multiple organs, as a lack of knowledge can impede a proper diagnosis.

Case: We present a case of a 61-year-old male admitted with a diagnosis of acute appendicitis confirmed on CT. The patient presented with a 3-day history of fever, chills, severe abdominal pain and nausea. The patient was noted to have a non-tender, palpable mass in the right sartorius muscle. An MRI of this lesion suggested it to be a sarcoma. Despite antibiotic therapy, the patient become progressively septic and developed respiratory failure along with severe thrombocytopenia. Despite ventilator support, the patient passed away after several minutes of CPR. The cause of death was attributed to a fatal cardiac arrhythmia due to primary systemic anaplastic large cell lymphoma involving the heart, lungs, spleen, liver, and right sartorius muscle. The patient was also diagnosed with early acute appendicitis without perforation.

Conclusion: Our patient was in Stage IV anaplastic large cell lymphoma, as he had non-contiguous extralymphatic involvement. Due to the rarity of cardiovascular involvement of systemic anaplastic large cell lymphoma, there is limited data regarding the management and treatment. However, early detection of cardiac infiltration with appropriate diagnostic methods is crucial for a favourable outcome

Keywords: Appendicitis; Anaplastic Large Cell Lymphoma; Cardiac Involvement

Abbreviations: NK: Natural Killer Cells; ALCL: Anaplastic Large Cell Lymphoma; ALK: Anaplastic Lymphoma Kinase IPI: International Prognostic Index OS: Overall Survival; PFS: Progression-free survival

Background

Non-Hodgkin lymphomas consist of hematologic malignancies of various origins, such as B cell progenitors, T cell progenitors, mature B cells, mature T cells, and, rarely, natural killer cells (NK) [1]. Anaplastic large cell lymphoma (ALCL) is a lymphoid neoplasm that develops from T cells or NK cells. ALCL comprises approximately two percent of all Non-Hodgkin lymphomas [2] and accounts for 16 percent of T cell lymphomas [3]. ALCL occurs as both a primary cutaneous and primary systemic variant [3]· While morphologically alike, these forms are distinct entities of ALCL. Primary cutaneous ALCL appears on the skin of patients in the form of raised lesions [3]· As the name suggests, primary systemic ALCL presents as an extracutaneous disease. Patients with systemic ALCL are categorized as either anaplastic lymphoma kinase (ALK) positive or negative [2]. Extranodal infiltration occurs in twenty percent of patients with systemic ALCL, with bone, stomach, lung, liver, and skin acting as common extranodal sites of involvement [2]. However, little is known regarding cardiovascular involvement of systemic ALCL. As this case depicts, it is vital for surgeons to be aware of the complex properties of ALCL involving multiple organs, as a lack of knowledge can impede a proper diagnosis.

Case Presentation

An otherwise healthy 61-year-old male Jehovah's Witness was admitted overnight to the surgical service by the emergency

department physician with a diagnosis of acute appendicitis. The patient had presented with a 3-day history of fever, chills, nausea, and severe abdominal pain. On physical examination the patient was noted by the emergency physician to be tachycardic with a maximum temperature of 38.3°C, and to have lower abdominal tenderness on palpation without signs of peritonitis. The cardiovascular and respiratory examinations were otherwise unremarkable. The lab work was normal save for thrombocytopenia with platelets of 83, and a mild elevation in CRP (17). The chest x-ray was normal and a CT scan of the abdomen and pelvis demonstrated a mildly dilated appendix measuring 10mm without surrounding fat inflammation, suggesting early tip appendicitis. The patient was started on broad-spectrum antibiotics. When assessed by the surgical service in the morning, the patient was noted to have a non- tender, palpable mass in the right medial thigh and no significant abdominal tenderness. A venous Doppler ultrasound was ordered to exclude DVT, as well as a CT angiogram to assess for pulmonary embolus. Imaging failed to demonstrate any thrombus or emboli; however, a complex mass in the sartorius muscle measuring 2.4x1.0x1.4 cm with ill-defined margins and increased vascularity was noted. A repeat contrast-enhanced CT of the pelvis and upper thigh performed the following day confirmed these findings in the sartorius muscle, but also found ongoing appendiceal enlargement with a possible appendicolith. Over the following two days the patient remained tachycardic and febrile with temperatures reaching above 40°C. Repeated laboratory tests revealed persistent low platelet count and the development of a mild microcytic anemia with a hemoglobin of 115g/L with MCV of 74. The serum CRP increased to 48, and total white blood cells increased to 14.6. An arterial blood gas showed respiratory alkalosis with a pH of 7.52, a pCO2 of 25, a pO2 of 54 and a bicarbonate level of 20. The patient's troponin level rose from 71 to 1083 ng/L indicating myocardial damage, along with an elevated D-Dimer (>4000ug/L). Hepatitis A, B, and C tests, as well as testing for HIV and malaria smear, were all negative. A urinalysis was positive for a small number of leukocytes. A repeat chest x-ray showed a hazy perihilar opacification and vascular re- distribution consistent with worsening pulmonary edema or possible infection. A lumbar spine MRI failed to show evidence of epidural abscess, destructive osseous, osteomyelitis or discitis. A MRI of the lower right extremity suggested that the lesion in the sartorius muscle was a sarcoma. A transthoracic echocardiogram demonstrated a standard biventricular size and systolic function, no chamber enlargement, no pericardial effusion and no significant valvular disease.

Five days after admission, the patient's condition continued to deteriorate with no clear diagnosis. He remained thrombocytopenic and febrile with temperatures over 40°C. Testing for Epstein-Barr virus and cytomegalovirus were both negative. Due to worsening respiratory failure the patient was intubated and transferred to a tertiary centre ICU. The patient required increasing oxygen and expiratory pressures from a ventilator. An x-ray initially displayed characteristics of 4 quadrant airspace disease, indicating left-sided pneumonia but this theory was quickly discarded once the patient improved 24 hours later. His urine, stool and blood cultures remained negative. There was no evidence of microangiopathic hemolytic anemia or uremia to indicate thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. The patient remained thrombocytopenic with no clear etiology, while other cell lines did not decline. The patient's condition worsened over the following four days, despite proning, broad-spectrum antimicrobial therapy, renal replacement therapy, continuous catecholamine support and ventilator support. Following several minutes of CPR, the patient passed away nine days after his initial admission.

An autopsy was conducted. The cause of death was attributed to a fatal cardiac arrhythmia due to primary systemic ALCL involving the heart, lungs, spleen, liver, and right sartorius muscle. The colonization of these locations explains the patient's respiratory failure and abnormal heart rate. Lung samples did not contain any respiratory viruses or bacteria. However, there were diffuse interstitial infiltrates of atypical cells with lymphoid morphology and apoptotic bodies. The malignant cells expressed CD30 and CD45 and were negative for pankeratin stains, S100, SOX10, Melan-A, CD3, CD5, and CD20. These results are in accordance with ALCL. Infiltrates of ALCL were also seen in the hilar lymph nodes. Mixed inflammatory cells of a lymphohistiocytic nature invaded the heart, some demonstrating marked nuclear atypia. A special stain test of the atypical cells was positive for CD30 and CD45, while negative for S100, CD3, CD5, and CD20, confirming the infiltration of ALCL in the heart. Samples of the sinoatrial and atrioventricular nodal regions also consisted of atypical cells compatible with ALCL. CD30- positive cells scattered the spleen and liver. Hemorrhage and necrosis were observed in areas of the spleen, which were lined with atypical cells. Atypical cells compatible with ALCL were also identified within lymphovascular spaces. The mass in the sartorius muscle was predominantly composed of chronic inflammatory infiltrates and vascular channels. CD30 and CD45-positive atypical cells were found within the inflammation, confirming colonization by ALCL. No tests were performed to confirm the patient as ALK-positive or ALK-negative. The patient was also diagnosed with early acute appendicitis without perforation.

Discussion and conclusion

A multi-authored case report discussing ALCL, published in 2021, found only 10 reported cases of primary systemic ALCL with cardiovascular involvement [4]. Consequently, there is limited data regarding the management and treatment of cardiovascular ALCL. However, early detection of cardiac infiltration with appropriate diagnostic methods is crucial for a favourable outcome. The medical diagnostic examination suggested for patients with possible primary systemic ALCL would include a history and physical exam with attention to the skin, lymph nodes, abdomen, head, and neck as well as to identify the patient's performance status and any presence of B symptoms. Further recommended investigations include CBC, LDH, metabolic panel, uric acid test, and a bone marrow biopsy with or without aspiration. The imaging recommendations include a PET or CT scan and an echocardiogram

or MUGA scan. A calculation of the International Prognostic Index (IPI) is also suggested. Other evaluations could be useful in selected cases, such as a CNS evaluation, HIV testing, Hepatitis B and C testing, and quantitation of Epstein Barr Virus by PCR amplification [5]. Treatment options differ depending on whether the patient expresses the ALK gene. Some options involve multiagent initial chemotherapy and CHOP chemotherapy (cyclophosphamide, doxorubicin hydrochloride, oncovin, and prednisone). The initial overall response rates are 77 percent [6] and 60-90 percent [7], respectively.

Patients aged over 60 with Stage I or II ALCL, normal serum LDH level, ECOG performance under two, and one or fewer extranodal sites have a good prognosis and are considered low- risk with an International Prognostic Index (IPI) of zero to one. Patients over 60 with Stage I or II ALCL, serum LDH above the normal, ECOG performance under two, and one or fewer extranodal sites have a good prognosis but are in the low-intermediate risk group, with an IPI of 2. Patients over 60 with Stage I or II ALCL, LDH above the normal, ECOG performance between two and four, and one or fewer extranodal sites have a poor prognosis and in the high- intermediate risk group with an IPI of 3. Finally, patients over 60 with Stage III or IV ALCL, LDH above the normal, and ECOG performance between two and four have a poor prognosis and are placed in the high-risk group with an IPI of 4-5, depending on the number of extranodal sites [5]. From a 2021 study of 150 patients with ALCL, those with a low IPI (0-2) had a five-year overall survival (OS) of 62 percent and a five-year progression-free survival (PFS) of 53 percent. Patients with a high IPI (2-4) had a five-year OS of 27 percent and a five-year PFS of 21 percent [6]. Our patient was in Stage IV ALCL as he had non-contiguous extralymphatic involvement. In conclusion, physicians should familiarize themselves with ALCL and consider the possibility of cardiovascular involvement in the differential diagnosis.

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