CASE REPORT

Fatal pulseless electrical activity in an African American man with natural killer/T-cell leukemia/lymphoma and myocardial involvement

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Received: August 17, 2015 **Accepted:** August 19, 2015 **Online Published:** August 25, 2015
DOI: 10.5430/crim.v2n4p10 **URL:** http://dx.doi.org/10.5430/crim.v2n4p10

Abstract

A 50-year-old previously healthy man presented with acute shortness of breath, fever, and back pain. Physical examination was normal. He rapidly developed hypoxemic respiratory failure requiring mechanical ventilation and pancytopenia. An extensive infectious work up was negative. After a gallium scan showed increased uptake in the lungs, he underwent bone marrow biopsy and open lung biopsy. The lung and bone marrow biopsies revealed Natural Killer/T-cell lymphoma/leukemia. Immediately after the open lung biopsy, the patient developed cardiac arrest with pulseless electrical activity from which he could not be resuscitated. At autopsy, he had extensive NK/T-cell lymphoma involving multiple organs, including the heart, lung, bone marrow, adrenal glands, and lymph nodes. The heart was the most prominently affected organ with involvement of the cardiac conduction system.

Keywords

NK/T-cell leukemia, NK/T-cell lymphoma, Lymphomatous cardiac infiltration, Aggressive non-Hodgkin's lymphoma

1 Introduction

Aggressive Natural Killer (NK)/T-cell lymphoma/leukemia is a very rare group of hematologic malignancies in adults. This neoplasm has a predilection for young Asian or Hispanic males typically in their 4th decade of life [1-8]. NK cell/T cell lymphoma/leukemia includes nasal NK/T-cell lymphoma, extra-nasal NK/T-cell lymphoma, aggressive NK/T-cell leukemia and blastic NK-cell lymphoma [3, 8]. Chemotherapeutic regimens used in other non-Hodgkin's lymphomas have not been shown to significantly improve outcomes. Due to the rarity of this malignancy, survival data have not been precisely established, but survival has been reported to be extraordinarily low [1, 3-5, 7]. Aggressive NK/T-cell leukemia/ lymphoma preferentially involves bone marrow and peripheral blood. Involvement of the myocardium, including the cardiac conduction system associated with cardiac arrhythmias, as in this case, has not been reported [12].

2 Case report

A 50-year-old previously healthy African American man presented to an outside facility with shortness of breath, fever and back pain after lifting a heavy object at work. Upon initial evaluation in their emergency department, the patient had a

normal complete blood count and no cause for his symptoms was found. He was discharged but returned three days later due to persistence of symptoms. He was then found to have pancytopenia and was empirically started on anti-microbial therapy with vancomycin, meropenem, levofloxacin, and fluconazole pending microbiological testing. Chest CT angiography was negative for pulmonary embolism but showed diffuse bilateral pulmonary infiltrates and emphysema. He rapidly developed acute hypoxemic respiratory failure requiring endotracheal intubation and mechanical ventilation.

Blood cultures, respiratory cultures, HIV and viral hepatitis serologic tests were negative. Antibiotics were discontinued on hospital day 9. Bone marrow biopsy showed marrow necrosis without granulomas, leukemic blasts, areas of fibrosis, or viral inclusions. The patient was then transferred to our facility for a higher level of care due to persistent respiratory failure, pancytopenia, and anuric acute renal failure.

The patient was married without children. He had smoked 1 pack of cigarettes per day for many years and only rarely drank alcohol. He did not use illicit drugs. The patient's mother had diabetes mellitus and an unknown form of cancer. He was employed at a factory that made laundry detergent.

Physical examination upon transfer to our facility revealed a mechanically ventilated, ill-appearing African American man. His heart rate was 94 beats per minute, blood pressure was 128/84 mmHg, respiratory rate was 35 per minute, and temperature was 97.7ºF. SpO_2 was 81% on a FiO_2 of 50%. He was orally intubated and sedated, with conjunctival icterus and coarse breath sounds which were more prominent in the right lung on anterior auscultation. He had copious tan respiratory secretions. He had a distended and tense abdomen with normal bowel sounds and no hepatosplenomegaly. His cardiac, cutaneous, and genital exams were all within normal limits.

The laboratory exam revealed pancytopenia with a white blood cell count of 510 per mm^3, hemoglobin level of 8.2 g/dl, and platelet count of 14,000 per mm^3(see Table 1). The BUN level was 86 mg/dl and the serum creatinine level was 6.73 mg/dl. Serum aspartate aminotransferase was 714 U/L, alanine aminotransferase 131 U/L, alkaline phosphatase 237 U/L, and the total serum bilirubin level was 16.1 mg/dl. An electrocardiogram performed shortly after the patient's admission showed a normal sinus rhythm, a prolonged QTc interval at 509 msec, and an age-indeterminate inferior-posterior infarct pattern (see Figure 1). Echocardiography, performed three days after transfer, showed a left ventricular ejection fraction of 60%-65% with normal left ventricular systolic function, mildly increased septal wall thickness, mildly increased posterior wall thickness, and left ventricular diastolic dysfunction.

Table 1. Laboratory values upon transfer to our facility

White Blood Count	0.51 k/µl	Sodium	137 mmol/L	PT	14.5 secs
Red Blood Count	2.91 M/µl	Potassium	5.2 mmol/L	aPTT	37.3 secs
Hemoglobin	8.2 g/dl	Chloride	106 mmol/L	INR	1.1
Hematocrit	23.2%	CO_2	16 mmol/L	Serum Fibrinogen	427 mg/dl
Platelet Count	14 k/µl	Anion Gap	16 mmol/L	FiO2	50%
Neutrophils (%)	0.24 k/µl (47%)	Creatinine	6.73 mg/dl	Arterial pH	7.31
Lymphocytes (%)	0.22 k/µl (43%)	Albumin	1.7 g/dl	Arterial pCO_2	33.6 mmHg
Bands (%)	k/µl (2%)	Alkaline Phosphatase	237 U/L	Arterial pO_2	189.9 mmHg
Anisocytosis	Slight	AST	714 U/L	Arterial HCO_3^-	16.6 mmol/L
Poikilocytosis	Moderate	ALT	131 U/L		
Target Cells	Few	Bilirubin, total	16.1 mg/dl		
Ovalocytes	Few	Bilirubin, direct	11.8 mg/dl		
Burr Cells	Moderate	BUN	86 mg/dl		
Shistocytes	Few	Blood Glucose	208 mg/dl		
Teardrop Cells	Slight				
Döhle Bodies	Present				

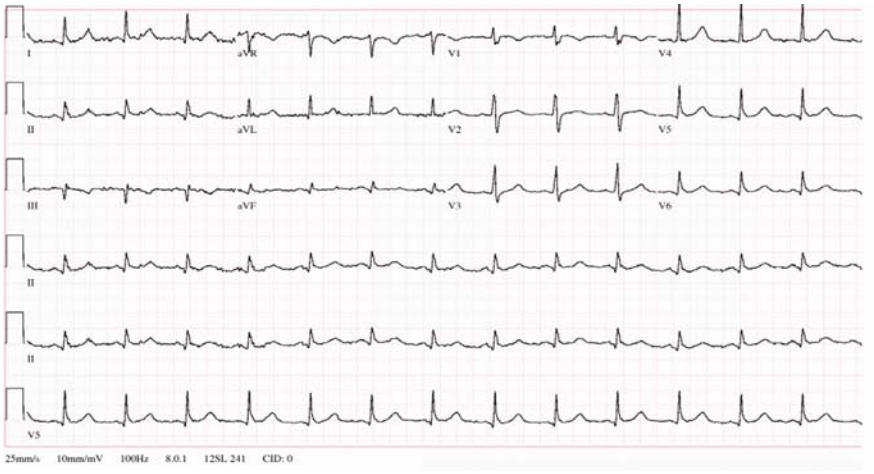

Figure 1. Electrocardiogram. Abnormal electrocardiogram showing a normal sinus rhythm with a prolonged QTc interval of 509 msec and an age indeterminate inferior-posterior infarct pattern. There was no evidence of myocardial infarction at autopsy, but there were several pale areas in the myocardium representing lymphomatous infiltration

He was initiated on continuous venovenous hemodialysis and an infectious work up was repeated due to recurrent and persistent fevers up to 104°F. He was restarted on meropenem. Fifteen days after transfer to our facility, he self-extubated, but continued to require 10-14 liters of oxygen per minute by Venturi mask. Repeat bone marrow biopsy was performed on hospital day 18 (after transfer) which again revealed extensive marrow necrosis with only focal viable cellularity. The marrow with focal viable cells was replaced by an infiltrate of small to medium sized lymphoid cells with marked atypical cellularity (see Figure 2A). Frequent mitotic figures were noted.

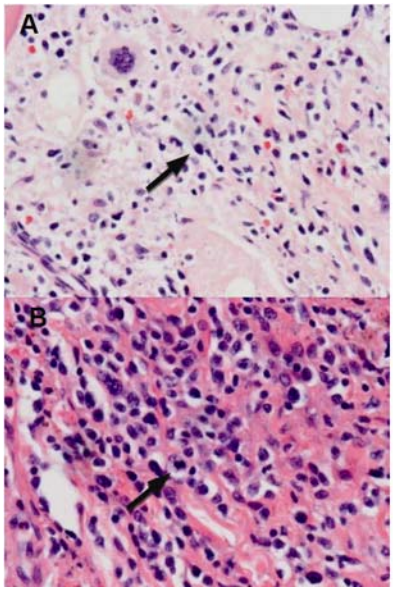

Figure 2. Histopathology of tissues after biopsy. (A) Bone marrow biopsy, high power. Hematoxylin and eosin stain. Atypical lymphoid cells of small to medium size are present (arrow). On immunostains (not shown), neoplastic cells were positive for CD2, CD3, CD56, TIA-1, and Ebstein-Barr virus encoded RNA (EBER) by in situ hybridization, confirming the diagnosis of aggressive NK/T-cell lymphoma; (B) Open lung biopsy, high power. Hematoxylin and eosin stain. Tumor cells showing increased mitotic activity (arrow). These cells showed the same immunostaining pattern as the bone marrow cells

Gallium scan showed increased uptake in the lungs, consistent with infection or malignancy. An open lung biopsy was performed 30 days after transfer with the hope of defining a specific diagnosis (see Figure 2B). Immediately posto-peratively, the patient developed hypotension with pulseless electrical activity and was unable to be resuscitated.

Final pathology from the aforementioned bone marrow biopsy and the open lung biopsy were diagnostic of a Natural Killer (NK) cell/T-cell lymphoma/leukemia that was Epstein-Barr virus-encoded messenger RNA (EBER)+, CD2+, CD3+, and CD56+.

Post mortem evaluation was performed to evaluate the extent of neoplastic disease and cause of death. Microscopic evaluation showed extensive infiltration by tumor cells with similar features to those noted on the bone marrow sample. Widespread involvement of almost every organ system was identified, with the heavier tumor infiltrates seen in the heart, bone marrow, lymph nodes, lungs, adrenal glands, and soft tissue around the seminal vesicles. The heart was the most severely affected (see Figure 3), including the cardiac conduction system. The myocardium, endocardium, and epicardium had lymphomatous infiltration. There was also 75 ml of serosanguinous fluid in the pericardium. Diffuse tan areas throughout the left ventricular myocardium and interventricular septum were seen on gross examination. The left ventricular wall thickness was 2.0 cm and the interventricular septal thickness was 2.5 cm. There was moderate coronary artery atherosclerosis without evidence of frank myocardial infarction.

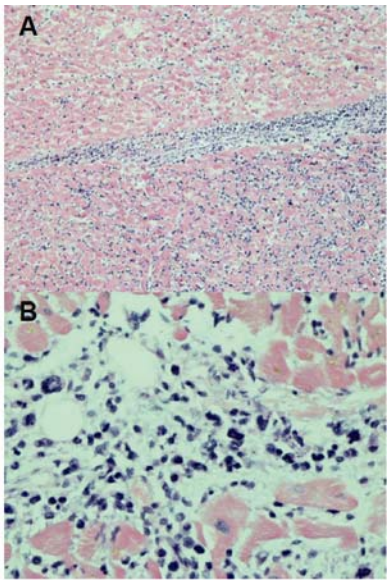

Figure 3. Histopathology of heart muscle at autopsy. (A) Myocardium, low power. Hematoxylin and eosin stain. Significant infiltration of NK/T-cell lymphoma cells into the myocardium; (B) Myocardium, high power. Hematoxylin and eosin stain. Extensive atypical lymphoid infiltrate involving the myocardium

3 Discussion

NK/T-cell lymphoma/leukemia is a very rare hematologic malignancy typically found in young adult males typically of Asian or Hispanic descent. Thus, our middle-aged African American patient is atypical demographically. Subtypes of CD56+ lymphoma include nasal-type NK/T-cell lymphoma, non-nasal NK/T-cell lymphoma, aggressive NK/T-cell leukemia/lymphoma, and blastoid NK-cell lymphoma [8]. The most commonly studied subtype of NK/T-cell lymphoma or leukemia is the nasal NK/T-cell lymphoma, which comprises up to 90% of all NK/T-cell lymphomas [6].

The most common sites of involvement are the bone marrow and peripheral blood. However, other sites of involvement may be seen [9]. Cardiac infiltration by NK/T-cell lymphoma has the potential to disrupt the cardiac conduction system and therefore lead to fatal cardiac arrhythmias.

Primary cardiac lymphomas are very rare and often do not have sites of metastases. They are more likely to be B-cell lymphomas and are found in the right atrium and right ventricle. Furthermore, up to 20% of disseminated lymphomas may have cardiac involvement [10].

Few case reports have described significant involvement of the myocardium by NK/T-cell lymphoma. Lepeak *et al*. reported a 54-year-old man with biopsy-proven, primary nasal type, extranodal NK/T-cell lymphoma presenting as a right atrial mass and with infiltration of the left and right ventricles. The patient also had tachyarrhythmias related temporarily to cocaine intoxication. His lymphoma was unresponsive to chemotherapy and radiation and proved to be fatal. He had progressive involvement of his gastrointestinal system and inferior vena cava by the lymphoma [11].

Baek *et al.* described a 23-year-old South Korean man with an extranodal pancreatic, nasal type, CD-56 negative NK/T-cell lymphoma who developed premature ventricular complexes and eventually ventricular tachycardia, possibly originating in the right ventricle, during his chemotherapy treatment with ifosfamide, methotrexate, etoposide, and prednisone. It was postulated that the patient's cardiac arrhythmias were due to infiltration of the lymphoma into the right ventricular myocardium [12].

Kanesvaran *et al*. described a 65-year-old Asian man who was found to have CD-56 negative extranodal nasal-type NK/T-cell lymphoma with bone marrow involvement. Left ventricular systolic function was depressed with an ejection fraction of 25%-30%. It was thought that the patient had lymphomatous infiltration of the right atrium with subsequent supraventricular tachycardia and atrial fibrillation that was treated with amiodarone [13].

Kuwabara *et al*. described a fatal, CD56+, EBV+ nasal type NK/T cell lymphoma primarily involving the orbit. At autopsy, there was extensive angiocentric metastases to the heart involving the myocardium and pericardium (with a 250 ml pericardial effusion) and also involving many other organs [14].

Aggressive NK/T-cell lymphoma/leukemia is uniformly resistant to conventional regimens used to treat aggressive non-Hodgkin's lymphomas [1, 15]. Patients with aggressive NK/T-cell leukemia/lymphoma typically present with advanced disease and are very ill with fever, weight loss, night sweats, lymphadenopathy, hepatosplenomegaly, multiorgan failure and, rarely, with a hemophagocytic syndrome which includes cytopenias and prolonged fevers [1, 17]. Our patient exhibited hypoxemic respiratory failure, acute renal failure, pancytopenia, and severe liver dysfunction. Other clinical presentations of aggressive NK/T-cell leukemia/lymphomas have included involvement of the bone marrow, gastrointestinal tract and skin [1]. Cardiac involvement, as in our case, is very rare [11-14]. Diagnosis of this hematologic malignancy is made by review of a peripheral blood smear, bone marrow morphology, histopathology and flow cytometry. Bone marrow necrosis can be a helpful diagnostic clue in patients with NK/T cell lymphoma (as in our patient), but is not found in all presentations [1, 5]. Our patient never received chemotherapy for his lymphoma due to his fatal cardiac arrhythmia and post-mortem diagnosis of the NK/T-cell leukemia/lymphoma.

Natural killer cells are lymphocytes that have potent antiviral and cytotoxic effects against newly acquired pathogens before the adaptive immune system is able to respond [18, 19]. The CD56 antigen is expressed on normal NK cells. The gene for CD56, which is also known as neural cell adhesion molecule 1 (NCAM1) and as MSK39, is located on chromosome 11 [21]. This gene encodes a cell adhesion protein which allows for cell-cell interactions and is important in the development of T cells, the nervous system and dendritic cells [19]. It is a member of the killer immunoglobulin superfamily which recognizes MHC class I receptors and is important in the release of cytokines, such as IFN-ɣ, IL-13, IL-10, TNF-α, and TNF-β [19-21]. CD56 expression is an uncommon finding in most other non-Hodgkin's lymphomas. Aggressive NK/T-cell lymphomas typically express not only CD56, but also CD2, CD3ε, and EBV [1, 3, 5, 7-9, 16, 17]. Expression of CD56 and positivity for EBV is a poor prognostic factor in aggressive lymphomas and is associated with disease that is often resistant to treatment [15].

In 49 Chinese patients with extranasal, CD56+, non-B-cell lineage lymphomas, Chan *et al*. reported that the most common subtype resembled the nasal type NK/T-cell lymphoma (34 patients, or 69%) [8]. The neoplastic cells were pleomorphic with irregular nuclei and granular chromatin with the following immunophenotype: CD2+, CD3/Leu4-, CD3ε+, and, almost always, EBV+. Patients with the aggressive extranasal NK cell leukemia/lymphoma subtype were less common (n=5, or 10%). These neoplastic cells had round nuclei and azurophilic granules in a pale cytoplasm with the following immunophenotype: CD2+, CD3-, CD16-, and, invariably, EBV+. All 5 of these patients died within 6 weeks of diagnosis. The remaining 10 patients with CD56+ lymphomas had even rarer EBV negative subtypes [8].

The International T-cell lymphoma project compiled 1,314 cases of either peripheral T-cell lymphoma or natural killer T-cell lymphoma. NK/T-cell lymphoma accounted for only 10.4% of the cases (4%-5% of the cases in North America and Europe and 22% of the cases in Asia). With regard to the extranasal NK/T-cell leukemia/lymphoma cases, their median

age was 44 years and 68% of patients were male. Most of them presented with stage III/IV disease (69%); only 18% had a positive bone marrow examination. Survival of patients with NK/T-cell leukemia/lymphoma was poor with standard lymphoma treatment regimens (5 year overall survival, 9%; 5 year failure-free survival, 6%) [2]. Our African-American patient's immunophenotype, as well as his clinical course, is most consistent with the aggressive NK/T-cell leukemia/lymphoma as described by Chan *et al.* in their 5 Chinese patients [8].

Due to the extraordinarily rare nature of NK/T-cell leukemia/lymphoma, treatment options are not well established and the mortality rate is very high, especially within the first days to weeks of presentation [1, 7, 9]. Multidrug chemotherapy has not been shown to improve outcomes due to the very aggressive nature of this disease. Proposed treatment options include cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) [1, 4, 7]. Unlike nasal NK/T-cell lymphoma, mortality rates have not been well defined for non-nasal aggressive NK/T-cell leukemia/lymphoma but remain exceedingly high, especially within the first 6 weeks to two months, often due to multisystem organ failure [1-3, 5, 6, 9].

Our patient experienced pulseless electrical activity directly after an open lung biopsy. Common causes of pulseless electrical activity include acute coronary occlusion, hypoxemia, hypovolemia, pulmonary embolism, and severe metabolic derangements which lead to electrical impulses that are unable to generate enough electrical potential to depolarize the myocardium [22]. In this case, the patient did not have evidence of severe cardiac compromise, a pulmonary etiology or severe metabolic abnormality during the pre-operative or post-operative course or at autopsy. Based on the clinical course and the findings on autopsy, the patient's most likely cause for his cardiac arrest and death was lymphomatous spread of the NK/T-cell lymphoma into his myocardium and cardiac conduction system.

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