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Case Report

Diagnosing a Rare Cutaneous Presentation of Anaplastic Large Cell Lymphoma

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Abstract

Anaplastic Large Cell Lymphoma (ALCL) is a rare aggressive neoplasm. Rapid and progressive lymphadenopathy is common. Due to its aggressive nature, two-thirds of initial presentations are in stage III or IV. Multifocal disease that is primarily cutaneous is rare and extracutaneous spread of the cancer occurs in up to 13 percent of cases.

In this case, a patient with systemic ALCL went undiagnosed for two months across three hospitalizations. A 33-year old male presented with multiple cutaneous lesions that had erupted bilaterally on his lower extremities and a fever which was unresponsive to over the counter medication.

The patient required three hospitalizations and extensive work up before a diagnosis of Anaplastic Lymphoma Kinase (ALK) -negative CD30+ T-cell lymphoma was made by skin and lymph node biopsy. Diagnosis was delayed due to this patient's uncommon presentation, the broad list of differential diagnoses, inaccuracies in biopsy, and communication delays from multiple hospital visits. This patient had aggressive ALCL and passed away during the first week of chemotherapy treatment.

When there is a concern for malignancy, properly performed biopsies are important to collect from appropriate sites with non-necrotic tissue. Additionally, this case demonstrates the consequences of inadequate communication during handoff between transfer centers. It is important to have a broad differential diagnosis as well as prompt investigation and constant communication between all providers involved when a patient presents with abnormal and aggressively progressing symptoms.

Keywords: Diagnosis; Non-hodgkin t-cell lymphoma; Extranodal involvement; Cutaneous lesions; Biospy

Case Presentation

A 33-year old male with a past medical history of congenital deafness presented to an outside hospital with an un responsive fever and multiple cutaneous lesions that had erupted bilaterally on his lower extremities over the last month, some of which had started to cause extreme pain. He was admitted to Hospital Medicine for work up of the progressive nodules.

During this hospitalization, he received a Computed Tomography (CT) of the chest, which revealed a subpleural nodular opacity in the left upper lung that was 1.6x1.3 cm as well as numerous liver lesions. He was found to have fecal occult blood positive stool and mild anemia, which was investigated with a colonoscopy where polyps were removed from his colon. However, throughout this hospitalization, no official diagnosis was made. He was discharged with follow up with Infectious Disease, Rheumatology, and Dermatology. The next week, he was noted to have a fever of 104°F in clinic and presented to the Emergency Department the following day.

Throughout this second hospitalization, the skin lesions progressed to fluid filled abscesses that ulcerated. Dermatology was consulted and a skin biopsy was performed which resulted in non-caseating granulomas. The patient was started on vancomycin and pipercillin-tazobactam but had recurrent fevers, worsening hypercalcemia, and continued progression of skin lesions so was transitioned to meropenem, azithromycin, and micafungin.

A repeat CT chest confirmed the presence of a left upper lobe nodular mass now measuring 2.5x2.3 cm without evidence of direct invasion into the mediastinum. Enlarged right hilar lymph nodes, hepatomegaly, and hepatic hemangiomas were also found. A bone marrow biopsy showed normocellular marrow, neutrophilia, and no identifiable malignancy. After this extensive investigation did not confirm a diagnosis, he was transferred to Ochsner Medical Center for higher level of care.

At Ochsner Medical Center, a multidisciplinary team including Infectious Disease, Rheumatology, Hematology/Oncology, Neurology, Dermatology, Pulmonology, and General Surgery were consulted for a full workup of a fever of unknown origin. Of note, the patient had hypernatremia (151mmol/L), hypercalcemia (14mg/dL), thrombocytopenia (63K/uL), and significant leukocytosis (61K/uL) on transfer admission.

The differential was broad, covering possible infectious, rheumatological, and hematological etiologies, and no clear diagnosis was evident. Initial testing included laboratory studies for viral,

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bacterial, and vasculitic causes*. However, all came back negative. For the third time in the three months since his initial presentation, Dermatology repeated punch biopsies, collecting from non-necrotic lesions.

A third CT again documented a left upper lobe consolidative opacity now measuring 5.4x4.3 cm, which was about double the previously measured length and width of 2.5x2.3 cm from 19 days prior. A CT Neck revealed bilateral axillary lymphadenopathy and a right cervical lymph node with central hypoattenuation compatible with necrosis. A second bone marrow biopsy was performed which still was negative for malignancy.

The patient continued to decline, was transferred to the Intense Care Unit, and was intubated for progressive tachypnea and airway protection. Vasopressor support was initiated. Stress dose steroids were started along with amphotericin B, voriconazole, and vancomycin while meropenem was continued. Continuous Renal Replacement Therapy (CRRT) was initiated due to progressively worsening oliguria and hypervolemia.

Finally, a diagnosis was made when pathology from the initial skin and axillary node biopsies revealed Anaplastic Lymphoma Kinase (ALK) -negative $CD30^+$ T-cell lymphoma on day 5 of this admission. The diagnosis was verified by an outpatient skin biopsy collected prior to the patient's second hospitalization that had not been included in the transfer paperwork which also came in on day 5 of admission, which also showed ALK-negative ALCL.

Cyclophosphamide was given as chemotherapy for the diagnosed lymphoma, but the patient continued to decline. Despite maximum ventilatory and hemodynamic support with vasopressors, the patient died within a week after he was transferred to Ochsner Medical Center, with progressive ALCL as the preliminary cause of death.

*HIV, EBV, CMV, syphilis, COVID-19 tests, acid-fact bacteria cultures, hepatitis serologies, p-ANCA, c-ANCA, ANA, urine electrophoresis, Blastomycoses, Histoplasma urine antibody tests.

Discussion

This case illustrates a clinical scenario in which a patient with systemic ALCL went undiagnosed for two months due to the various and yet unspecific clinical manifestations of this rare neoplasm.

Anaplastic Large Cell Lymphoma (ALCL) is a rare aggressive neoplasm that accounts for approximately 2 percent of adult non-Hodgkin lymphoma cases [1]. ALCL is a form of peripheral T-cell lymphoma that arises from mature T cells and is characterized by large lymphoid cells with pleomorphic nuclei. The age of incidence for primary systemic ALCL has a bimodal distribution with the first peak in the adolescent years and the second peak between the ages of 55-65 years [2]. This patient was 33 years old with initial presentation, much outside of the normal age ranges. Rapid and progressive lymphadenopathy is common, as are the classic B symptoms of fever, night sweats, and weight loss. Due to its aggressive nature, two-thirds of initial presentations are in stage III or IV and some patients present with extra-nodal manifestations of disease, particularly in the skin, liver, lung, or bone [3].

ALCL may present in the cutaneous form. This appears as nodules that can reach several centimeters in size and will form and grow over a few months; these nodules may also ulcerate. Multifocal disease that is primarily cutaneous is rare and extracutaneous spread of the cancer occurs in up to 13 percent of cases [4]. The patient initially presented to Dermatology clinic with cutaneous lesions, a rare extra-nodal manifestation of the ALCL. Due to the rarity of his presentation and the rate of progression, ALCL was not considered as a likely differential diagnosis.

ALCL can be classified as ALK-positive or ALK-negative, with ALK-negative cases having a worse prognosis [5]. Elevated LDH levels, high presenting stage, and ALK-negative status, all of which this patient had, have been associated with lower survival rates among ALCL patients. Furthermore, ALK-negative anaplastic T-cell lymphoma has been shown to have a 5-year overall survival rate of only 37% [5]. While ALK-positive ALCL is characterized by specific genetic features, ALK-negative ALCL has an ill-defined genetic landscape, which prevents effective therapeutic strategies from being developed for subgroups of patients [6].

The best way to diagnose ALCL is by performing an excisional tissue biopsy, typically from a lymph node [7]. An adequate tissue sample is necessary for classification of lymphoma, preferably from fresh tissue samples with less necrosis, as the necrotic tissue can obscure proper classification and delay diagnosis [8]. The second tissue biopsy that was conducted did not identify the malignancy, likely due to the inadequate amount of fresh tissue obtained which delayed diagnosis further. Both a lymph node biopsy and a non-necrotic skin biopsy were eventually able to confirm the diagnosis of ALK-negative ALCL for this patient. However, there were multiple negative or indeterminant biopsies prior to diagnosis.

Additionally, clear communication between medical centers and outpatient clinics is of the upmost importance. The patient in this case may have been able to receive appropriate treatment sooner had all past results and reports been included in the transfer. Due to incompatible electronic records systems, the outpatient clinic results had to be printed, scanned, and uploaded after specifically being requested. Transfer procedures need to be updated and clarified across systems for the safety of patient care.

However, by the time the diagnosis was confirmed, the patient had already progressed and his prognosis was poor. The patient received one dose of cyclophosphamide but passed away shortly after. The National Comprehensive Cancer Network (NCCN) guidelines state that participation in clinical trials is the preferred management approach for patients with ALK-negative ALCL due to small sample sizes and limited data assessing the impact of chemotherapy in this subgroup of patients [9]. If no clinical trials are available, the recommended chemotherapy approach is based on CD30 expression [10].

This patient passed away due to aggressive ALCL, having been undiagnosed for over two months and three hospitalizations. The cause for this delay in diagnosis was multifactorial including his rare and aggressive presentation, his nonspecific biopsies, and lack of communication between hospitals. Ultimately, given the high mortality rate of advanced disease, the delay in diagnosis was unlikely to have made a difference in the survival of this patient.

Conclusion

This case discusses a rare cutaneous presentation of ALCL. It also addresses the importance of quickly performing and analyzing sterile, properly performed biopsies when there is concern for malignancy. Additionally, this case demonstrates the consequences of inadequate communication during handoff between transfer centers. This patient had aggressive ALCL and due to his rare initial symptoms, inaccuracies in biopsies, and lack of communication between facilities, the patient passed away. It is important to remember to have a broad differential diagnosis as well as prompt and accurate investigation and constant communication between all providers involved when a patient presents with abnormal but aggressive progressing symptoms.

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