BAOJ Pharmaceutical Sciences

Emily Q Chen, et al., BAOJ Pharm Sci 2017, 3: 4
3: 047

Case Report

Impact of Steroid Monotherapy on the Presentation and Diagnosis of Aggressive Natural Killer-Cell Lymphoma: A Case Report

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Abstract

Aggressive natural killer-cell lymphoma (ANKL) is an extremely rare and catastrophic neoplasm that is steroid-responsive. We discuss the case of a 34-year-old Asian female with an unusual presentation of ANKL. She was admitted to our hospital with diagnosed tuberculosis of the eye with progressive vision loss and headache. She had been taking anti-tuberculous medications with prednisone 20 milligrams daily for two months prior to admission, at which time computerized tomography of the head did not show any acute abnormalities. Her clinical status deteriorated after discontinuation of prednisone, but improved after initiation of hydrocortisone 400 milligrams daily. Given their mild anti-inflammatory properties, corticosteroid therapy may complicate the diagnosis of ANKL and other steroid-responsive malignancies, and should be considered during the course of care.

Background

Aggressive natural killer-cell lymphoma (ANKL) is an extremely rare and catastrophic neoplasm of mature natural killer cells with a median survival of two months. With fewer than 200 cases reported worldwide, the definitive diagnosis remains unclear and relies predominantly on histology [1].

Exposure to corticosteroids may alter clinical presentation and further complicate the diagnosis [2-4]. Non-Hodgkin lymphoma (NHL) is highly steroid-responsive, with certain central nervous system (CNS) lymphomas showing dramatic improvement in enhancement, mass effect, and edema surrounding the tumor following dexamethasone use [3]. Treatment of NHL with corticosteroid monotherapy has even been used to provide temporary response [4]. However, little is known about corticosteroid monotherapy specifically in the treatment of ANKL.

Case

A 34-year old Asian female was admitted to our institution with a history of one to two months of vision change in the right eye and floaters seen in the left eye. As an outpatient, she was diagnosed with tuberculosis of the right eye and started on rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) treatment at unspecified doses, and prednisone 20 milligrams (mg) daily. She followed up with a specialized eye clinic, but reportedly developed elevated liver enzymes "in the thousands" (significantly above the upper limit of normal), and was therefore discontinued off RIPE therapy two to three weeks prior to admission at our institution. The day before her admission, prednisone was discontinued per her ophthalmologist and she was started on valacyclovir 1 gram per os

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Sub Date: December 19th 2017, **Acc Date**: December 30th 2017, **Pub Date**: December 30th 2017.

Citation: Emily Q Chen, Anna H Yang, Christopher Franzese, Daniel T Abazia (2017) Impact of Steroid Monotherapy on the Presentation and Diagnosis of Aggressive Natural Killer-Cell Lymphoma: A Case Report. BAOJ Pharm Sci 3: 47.

(PO) every 8 hours. She was admitted to our hospital with complaints of 48 hours of right-sided headache and dizziness with difficulty ambulating (gradual onset, constant, mild intensity). She had no other associated symptoms and a Glasgow Coma Scale (GCS) of 15.

In the emergency department, she was given one dose of intravenous (IV) dexamethasone 4 mg. Computerized tomography (CT) of the head showed no acute intracranial abnormalities at this time. She remained off steroid therapy but continued on acyclovir 670 mg IV every 8 hours. On day three of her admission, her neurological status suddenly deteriorated and she was transferred to the neurological intensive care unit (ICU) for further evaluation. Another CT of the head was negative for infarction and mass effect but the patient was noted to have increased hypodensity in the right lentiform nucleus, suspicious of an infectious/inflammatory process. Additionally, magnetic resonance imaging (MRI) of the head showed signal abnormality involving the right basal ganglia/internal capsule, dorsal pons, right dorsolateral medulla and left upper cervical cord. During this time, the patient was afebrile, progressively lethargic but cooperative, and receiving ongoing tuberculosis medications. She was also resumed on prednisone 10 mg PO daily.

Clinical Deterioration with Prednisone 10 mg PO Daily

On days one through three of prednisone therapy, the patient continued to decline clinically, presenting with left-sided hemiplegia, worsening lethargy and dysarthria, increasing rash, and new onset fever >102.8° F. The patient's immune status showed a T-cell deficiency with a CD4 count of 300 cells/mm^3, but it was unclear at this time whether this was due to steroid treatment, congenital disease, or in the setting of tuberculosis. On days four through five of prednisone therapy, the patient's fever persisted and she became hemodynamically unstable, requiring blood pressure support with norepinephrine 8-12 micrograms (mcg)/min IV infusion. CT of the head and MRI of the brain with and without contrast showed progressive abnormal enhancements extending from the right subthalamus and corticospinal tract to the left corticospinal tract, right basal ganglia, dorsal and ventral pons and medulla, and into the upper cervical spinal cord. CT of the abdomen also showed bilateral adrenal masses of unknown etiology, and these masses were biopsied for histology. On day six of prednisone therapy, the patient remained febrile and required more aggressive blood pressure support with an additional 1 liter IV bolus of 0.9% NaCl and norepinephrine 8-40 mcg/min IV infusion. Due to suspected adrenal insufficiency, she was placed on fludrocortisone 0.1 mg PO bis in die (BID).

Transient Improvement with Fludrocortisone 0.1 mg PO BID

On day 7 of prednisone therapy and day 2 of fludrocortisone therapy, the patient improved hemodynamically and required only intermittent hour-long infusions of norepinephrine at 2-8 mcg/min IV throughout the day. She continued to be febrile, but was noted to be more alert and following commands at this time. However, her left side remained severely paretic with no movement in her left leg. On day eight of prednisone therapy and day three of fludrocortisone therapy, the patient stopped following commands (GCS 7). Per recommendation by an endocrinology consult, the patient's prednisone was discontinued and she was initiated on hydrocortisone 100 mg IV every 6 hours.

Dramatic Clinical Improvement with Hydrocortisone 100 mg IV Every 6 Hours

After receiving hydrocortisone 100 mg IV every 6 hours for four days, the patient's neurological status improved dramatically and she was subsequently extubated. Her fever resolved, her norepinephrine drip was discontinued, and she became alert and began following commands once again. Unfortunately, despite this clinical improvement, the diagnosis for ANKL was made based on histology results. The patient was subsequently tapered down to hydrocortisone 75 mg IV every 8 hours for one day, followed by 50 mg IV every 8 hours for seven days. She was then transferred to a different institution for the management of ANKL.

Diagnosis of ANKL

Fine needle aspiration of the left adrenal mass showed atypical lymphoid cells, small to medium-sized with irregular nuclear contours and variably prominent nuclei. Immunohistochemistry showed cells positive for CD3, CD45, and Bcl-2 and negative for pancytokeratin, inhibin, S100, synaptophysin, CD5, CD20, CD23, CD10, Pax-5, Bcl-6, and cyclin D1. Ki-67 proliferation rate was high (80-85%). Flow cytometric analysis showed an atypical hematolymphoid population (CD2+, cytoCD3+, CD56+, HLA-DR+, C38+, CD45+). Tumor cells were positive for EBV by ISH stain. T-cell gene rearrangement was negative.

Cerebrospinal fluid examination showed an atypical T/NK-cell population. Tumor cells were immunoreactive for leukocyte common antigen CD45 (8.34%), CD2 (5.48%), CD7 (5.66%), bright CD38 (5.08%), CD56 (5.64%), and CD11c (3.56%). B cells were virtually absent.

Conclusion

Steroid use in this patient may have dampened the initial aggressive clinical course of ANKL. The mechanism of action is thought to be related to the induction of apoptosis through decreasing DNA, RNA, and protein synthesis in certain lymphoid populations [4-6]. However, the minimum dose required to induce this response has yet to be established. The standard steroid dose in effective NK/T lymphoma regimens such as dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) is dexamethasone 40 mg daily. Prednisone has also been used, with doses ranging from 60-100 mg/m^2/day for five days, although a lower threshold of prednisone use has not been determined [7].

In light of this, it is possible that the patient's initial eye lesion was not related to tuberculosis but rather a manifestation of lymphoma, with

commonly-observed clinical symptoms masked by chronic corticosteroid use. Upon presentation, the patient did not exhibit outward signs of a typically-aggressive lymphoma, and had been receiving prednisone 20 mg daily for at least two months. When prednisone was discontinued, her clinical status rapidly deteriorated and subsequently improved after initiation of hydrocortisone at a dose equivalent to roughly half that of the dexamethasone component of the SMILE regimen (**Table 1**). As this regimen is known to be associated with promising overall response [8-9], several days of high-dose hydrocortisone may have contributed to the patient's clinical improvement. In summary, the possible effect of corticosteroid therapy on clinical response may complicate the diagnosis of ANKL and other steroid-responsive malignancies, and should be considered during the course of care [10].

Table 1. Comparative anti-inflammatory activities of steroids[10]

	Anti-inflammatory potency	Patient's dose	Equivalent dexamethasone dose
Hydrocortisone	1	400 mg	15 mg
Prednisone	4	20 mg	3 mg
Fludrocortisone	15	0.2 mg	--
Dexamethasone	30	--	--

Acknowledgements

We are thankful to our colleagues Edgar Garcia-Morales, Hermann Schumacher, and Natalie Gofman for their expertise in caring for this patient, as well as Kim To for her guidance on this publication.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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