A case of aggressive natural killer cell leukemia

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Summary

A 23-year-old man presented with a 1-month history of a red and painful right eye, with visual acuity reduced to hand motions. Examination showed uveitis with keratic precipitates, cells and flare in the anterior chamber, and vitritis that obscured visualization of the right fundus. The following week, he was noted to have the following left-sided findings: reduced visual acuity (6/18), painless upper eyelid edema, an elevated, pink bulbar conjunctival lesion, limitation of ocular abduction, paresthesia in the V1 and reduced sensation in the V2 distributions. Blood tests showed pancytopenia. Results from the aspirate and trephine biopsy of his bone marrow were consistent with aggressive natural killer (NK) cell leukemia, a rare cause of ocular and periocular inflammation that requires a multidisciplinary team approach to care.

Case Report

A 23-year-old Māori man presented at Tauranga Eye Specialists with a 1-month history of red, painful, and watery right eye, and blurred vision. He had associated fevers, chills, cough, dyspnea, diarrhea with hematochezia, and widespread arthralgia. Past medical history was significant for hay fever, for which he occasionally took antihistamines. Examination showed unaided visual acuity of hand motions in the right eye and 6/12 in the left eye, with no improvement on pinhole. The right eye had conjunctival injection, small and large keratic precipitates, 2 to 3+ cells in the anterior chamber with 2+ flare, and vitritis obscuring the fundal view. B-scan ultrasound showed a flat retina. Examination of the left eye was normal.

The initial impression was severe, right eye, acute anterior and intermediate uveitis. He was started on topical prednisolone acetate 1% hourly, cyclopentolate 1% three times daily, and dexamethasone ointment nightly to the right eye.

On review the following week, he had also developed reduced visual acuity in his left eye
(6/18, with no improvement on pinhole), a painless, edematous left upper eyelid without
erthema, and an inflamed left plica semilunaris (Figure 1). He had paresthesia in the left V1 and
reduced sensation in the left V2 distributions and moderate limitation of abduction of the left
eye. He also had an elevated, pink lesion on the left superior bulbar conjunctiva. Visual acuity in
his right eye remained hand motions, with ongoing uveitis. Koeppe and Busacca nodules were
noted on the right iris. There was no evidence of uveitis in the left eye.

Investigations showed leukopenia (2.1 × 10⁹/L [normal, 4-11 × 10⁹/L]), neutropenia (0.8
× 10⁹/L [1.9-7.5 × 10⁹/L]), thrombocytopenia (51 × 10⁹/L [150-400 × 10⁹/L]), abnormal liver
function tests (alanine aminotransferase 607 U/L [<55 U/L], aspartate aminotransferase 170 U/L
[0-50 U/L], alkaline phosphatase 117 U/L [40-110 U/L], and gamma glutamyltransferase 111
U/L [0-60 U/L]), and an elevated angiotensin converting enzyme (ACE) of 161 U/L (20-70 U/L).
Human leukocyte antigen B27, antinuclear antibodies, antineutrophil cytoplasmic antibodies,
syphilis serology (venereal disease research laboratory test), toxoplasma IgG and IgM and
QuantiFERON-TB Gold were negative. Cytomegalovirus (CMV) IgG was positive, and IgM
was negative. Epstein-Barr virus (EBV) IgG was positive. Chest and lumbar spine X-rays did not
show any evidence of hilar lymphadenopathy or sacroiliitis. A right anterior chamber
paracentesis was negative on microscopy and culture for bacteria, and polymerase chain reaction
testing for herpes simplex and varicella zoster viruses. As his ACE was significantly elevated,
the possibility of sarcoidosis was considered. He was therefore started on oral prednisone at 1
mg/kg daily.

Computed tomography (CT) of the head, orbits, chest and abdomen was performed
showing nonspecific, soft tissue stranding and hyper-enhancement around the left globe and
extraocular muscles and mild splenomegaly. No radiographic features of sarcoidosis or
lymphoma were identified. Magnetic resonance imaging (MRI) scan of the head and orbits showed thickening of the left extraocular muscles and lacrimal gland (Figure 2).

Repeat blood tests showed worsening pancytopenia, with anemia (hemoglobin 75 g/L [normal, 130-175 g/L]), neutropenia (0.4 × 10^9/L [1.9-7.5 × 10^9/L]), lymphopenia (0.7 × 10^9/L [1-4 × 10^9/L]), and thrombocytopenia (14 × 10^9/L [150-400 × 10^9/L]).

Biopsy of the left superior conjunctival lesion showed a nonspecific, mixed inflammatory infiltrate and a granuloma. His case was reviewed by the hematology service, who then performed an aspirate and trephine biopsy from his bone marrow, which revealed hemophagocytosis and an increased population of natural killer (NK) cells (Figure 3), consistent with aggressive NK cell leukemia (ANKL). Treatment with steroids, methotrexate, ifosfamide, L-asparaginase, and etoposide (ie, SMILE chemotherapy regimen) was initiated.

At his last ophthalmology review, the anterior chamber inflammation had resolved. However, visual acuity in his right eye was light perception because of a dense cataract. Visual acuity in his left eye was 6/9 (unaided, with no improvement on pinhole).

**Discussion**

ANKL is a malignant proliferation of mature NK cells, accounting for <0.1% of all lymphoid neoplasms. It mainly affects those between 20 to 50 years of age, with a median age of 37 years and a slight male preponderance. It is more prevalent in Asia and Central and South America. There is a strong association with EBV, with 90% of ANKL cases being positive. The main clinical features are fever, hepatosplenomegaly, and hematological abnormalities, including hemophagocytosis and disseminated intravascular coagulation. Diagnosis involves integrating the clinical features, sites of involvement (predominantly the peripheral blood, bone marrow, liver, and spleen), and cellular characteristics, including morphology and immunophenotyping.
Although there is no universally accepted treatment approach,\textsuperscript{2} the SMILE chemotherapy regimen has shown some efficacy.\textsuperscript{1,3} Hemopoietic stem cell transplantation may also extend survival.\textsuperscript{1,2} However, the overall prognosis of ANKL is poor, with a median survival of less than one year.\textsuperscript{1}

Although leukemia is known to cause ocular inflammation,\textsuperscript{5} to our knowledge, this is the first case reported in the literature of uveitis secondary to ANKL, which likely relates to the rarity of this disorder. Extraocular muscle involvement in ANKL has been reported in one other case, with abduction limitation due to lateral rectus muscle infiltration.\textsuperscript{2} The current case highlights the importance of investigating for underlying causes when the ocular inflammation is atypical or severe and demonstrates the value of a multidisciplinary team approach to patient care.

**Literature Search**

PubMed was searched on February 20, 2021, without language restriction, using the following terms: *aggressive natural killer cell leukemia*, and *uveitis*. 
References


Figure 1. Left upper eyelid edema and inflammation with injection of the left plica semilunaris.

Figure 2. T1-weighted magnetic resonance image of the head and orbits with fat suppression and contrast. There is mild thickening of the left extraocular muscles (arrows) and left lacrimal gland (arrowhead), with abnormal enhancement of these structures and of the intraconal fat.

Figure 3. Immunohistochemistry staining of the patient’s bone marrow trephine biopsy. Natural killer cells show positive staining (brown) for the CD56 marker. Image courtesy of Dr. Helen Moore, Waikato District Health Board.