CASE REPORT

Gamma–delta T-cell lymphoma of skin, eye and brain presenting with visual loss

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SUMMARY

A young man presented with rapid, predominantly right-sided visual loss with a background of multifocal skin lesions. Visual acuity was right hand movements, left 6/5 Snellen, deteriorating to 6/38. He showed panuveitis with bilateral multifocal retinal infiltrates and retinal vasculitis. Multifocal brain lesions were identified. Biopsy of both skin and vitreous showed atypical lymphocytes, and immunohistochemistry confirmed T-cell lymphoma of gamma–delta subtype. Management with the CODOX-M/IVAC polychemotherapy regimen achieved rapid response including resolution of intraocular changes and substantial improvement of visual acuity to right 6/7.5, left 6/6. However, he relapsed before planned stem cell transplantation. Salvage with the gemcitabine/dexamethasone/cisplatin regimen, although temporarily effective, was followed by further relapse including widespread brain involvement, and he succumbed 10 months after presentation.

BACKGROUND

This is the first case of gamma–delta T-cell lymphoma to be reported with vitreoretinal involvement. The condition is aggressive and life threatening. Rapid diagnosis and treatment may be life-saving and sight-saving, but long-term prognosis remains poor.

CASE PRESENTATION

A 41-year-old Caucasian man presented with rapidly deteriorating vision in both eyes over 5 days.

Figure 1 The right fundus at presentation showing severe vitritis with widespread multifocal retinal infiltrations of variable size, particularly perivascular. Visual acuity: hand movements.

The right (R) eye saw hand movements only, the left (L) 6/5 Snellen, deteriorating to 6/38 within a few days. Ocular examination showed right panuveitis with severe vitritis, multifocal retinal infiltrates (particularly perivascular) and retinal arteriolitis (figure 1). The left eye showed fewer, better-defined white retinal deposits (figure 2). Fundal autofluorescence (figure 3) showed lesion enhancement, and optical coherence tomography of the R macula (figure 4) showed a thick, nodular plaque lesion in the outer retina. He was also noted to have multiple violaceous placoid skin lesions (figure 5). The itchy but painless skin lesions had been slowly spreading and enlarging for several months and the largest, on the left buttock, was 5.0 cm × 2.0 cm and apparently necrotising (figure 6). He was otherwise physically well but had chronic anxiety treated with mirtazapine and propranolol. Differential diagnosis included Behçet's disease, Sweet's syndrome, pyoderma gangrenosum, disseminated viral, bacterial or fungal infection or malignancy. He was commenced on empirical valacyclovir 1g three times daily, doxycycline 100 mg two times daily and penicillin V 500 mg four times daily.

INVESTIGATIONS

Investigations revealed a normal full blood count, normal liver function, an elevated creatinine to 120 µmol/L, C reactive protein (<1), ACE 43 IU/L, no autoantibodies, slightly raised IgA (3.22 g/L) with no paraprotein bands, normal chest X-ray, negative serology for syphilis, *Aspergillus*, *Streptococcus*, *Borrelia*, herpes simplex virus (HSV) I + II, HIV I + II, human T-lymphotrophic virus I + II and *Rickettsia*. Varicella zoster virus (VZV) IgG (but not IgM) was detected and PCR testing was negative for VZV, HSV I + II, cytomegalovirus and *Pneumocystis*.

MRI of head with angiography and contrast showed several distinct cerebral lesions involving the left cerebral peduncle and internal capsule, the splenium of the corpus callosum, ventricular trigones and left frontal pole, all suggesting neoplasia, with lymphoma being more likely than glioma on radiological grounds (figure 7A,B). Whole-body CT showed no lymph node enlargement, no bone lesions nor evidence of malignancy throughout the neck, thorax, abdomen or pelvis.

Diagnostic total vitrectomy was performed, the sample demonstrating atypical lymphocytes with pleomorphic nuclei, some with prominent nucleoli (figure 8). There were numerous cells undergoing apoptosis. Immunohistochemistry demonstrated

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Figure 2 The left fundus at presentation, with no vitritis but multifocal small well-defined retinal infiltrates.

Figure 3 Fundal autofluorescence of right and left maculas showing widespread lesion enhancement.

Figure 4 Optical coherence tomography of the right macula showing a thick nodular plaque at the chorioretinal interface.

that the atypical cells were positive for T-cell markers (CD2, CD3 (figure 9) and CD8>CD4) but CD5 was negative for CD20, CD10, CD23 and CD30. There was focal positivity for CD56 and the Ki-67 proliferation fraction was very high at 95%. There were some CD68-positive macrophages in the background. T-cell receptor clonality was confirmed by PCR, with evidence of a monoclonal gamma-delta T-cell population.

Incisional biopsy of the largest skin lesion was performed, histology showing nested aggregates of atypical lymphocytes with prominent tagging along the basal epidermis. In the deeper

Figure 5 One of several groups of itchy but painless violaceous skin lesions, this one on the thigh.

dermis, infiltrates were predominantly perivascular, without angioinvasion. There was also focal involvement of subcutaneous tissue. Immunohistochemistry demonstrated expression of CD2, CD3, CD56, T-cell-restricted intracellular antigen-1 granzyme B and S-100 by the atypical cells; CD4, CD5, CD7, CD8, CD20, T-cell receptor beta F1, CD30, TdT and CD123 were negative. In situ hybridisation for Epstein-Barr virus (EBV) was also negative. This immunoprofile excluded the diagnosis of mycosis fungoides which is the most common type of cutaneous T-cell lymphoma. The possibility of extranodal natural killer (NK) T-cell lymphoma could be considered although less likely as EBV was negative.

These features confirmed T-cell lymphoma, most likely of gamma-delta type, involving skin, eye and brain, a diagnosis confirmed at a supraregional lymphoma multidisciplinary meeting.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of uveitis with skin lesions includes sarcoidosis, tuberculosis, syphilis, Behçet's disease, Sweet

Figure 6 The largest skin lesion, on the left buttock, measured 5 cm x 2 cm and showed central crusting.

Figure 7 Horizontal (A) and coronal (B) T2-weighted MRI scans at presentation showing infiltration of left cerebral peduncle and internal capsule.

syndrome, Lyme disease, herpetic disease, disseminated bacterial or fungal infection or rarely, neoplasia. However, apparently necrotising skin lesions with zonal retinitis strongly suggests neoplasia, fungal infection or rickettsiosis. The differential diagnosis of cutaneous T-cell lymphoma includes mycosis fungoides, peripheral T-cell lymphoma not otherwise specified, extranodal NK T-cell lymphoma and CD30-positive T-cell lymphoproliferative disorders. There were excluded on morphological and immunophenotypical grounds.

TREATMENT

The patient was commenced on the CODOX-M/IVAC polychemo-therapy regimen (intravenous cyclophosphamide, doxorubicin, vincristine, high-dose methotrexate, alternating with ifosfamide, cytarabine and etoposide alongside intrathecal methotrexate and cytarabine), originally devised for Burkitt lymphoma but also used for high-grade non-Hodgkin's lymphoma involving the central nervous system (CNS) due to the incorporation of the CNS-penetrant agents methotrexate, cytarabine, ifosfamide and etoposide. Four cycles were administered to the patient over 3 months with no major complications.

Figure 8 Vitrectomy sample showing atypical lymphocytes with pleomorphic nuclei, some with prominent nucleoli and numerous apoptotic bodies.

Figure 9 Immunohistochemistry on vitrectomy sample demonstrating diffuse CD3 positivity by atypical cells.

OUTCOME AND FOLLOW-UP

Retinal infiltration and intraocular involvement resolved rapidly on treatment and within three cycles of chemotherapy, the patient's vision had improved to virtually normal (R 6/7.5, L 6/6). The retinal vasculitis resolved entirely with widespread areas of residual pigment epithelial atrophy, fortuitously with restored macular function ([figure 10](#)). The cutaneous plaques and necrotic buttock lesion resolved completely. Systemic restaging via fluoro-deoxyglucose-positron emission tomography-CT and MRI brain revealed a complete metabolic and radiological response. Unfortunately while awaiting consolidating syngeneic haemopoietic stem cell transplant (the patient had a twin brother), he underwent clinicoradiological progressive disease and salvage with the gemcitabine/dexamethasone/cisplatin regimen, although temporarily showing complete response, was followed by further intracerebral recurrence with widespread neurological deficit, and he died 10 months after presentation.

DISCUSSION

Intraocular lymphoma may be secondary to systemic lymphoma (in which cases lesions are usually discrete and choroidal rather

Figure 10 The right fundus after first-phase chemotherapy, 3 weeks after presentation, showing complete resolution of vasculitis, virtual elimination of retinal infiltration and widespread retinal pigment epithelial atrophy. Visual acuity: 6/7.5.

than retinal) or may arise within the eye (primary vitreoretinal lymphoma (PVRL), part of a presumed multicentric primary B-cell CNS and vitreoretinal malignancy). Intraocular lymphoma is increasing in incidence, but almost all cases are PVRL of large B-cell origin.¹ Typically this manifests as vitreous cellular infiltration mimicking inflammation and/or multifocal or coalescent intraretinal infiltrates. Primary vitreoretinal lymphoma of T-cell type is exceedingly rare² with approximately 20 cases in total being reported,² and the latest case series of 7 patients required contributions from 6 specialist centres in 5 countries.³ In contrast to systemic B-cell lymphomas involving the eyes that manifest usually in the choroid, T-cell malignancies tend to involve vitreous and retina, may also involve iris and optic nerve and may simulate uveitis. A review of 29 reported cases of primary and secondary T-cell lymphomas involving the eye⁴ in 2008 showed a mean duration of symptoms of 3.7 months before presentation, with 45% having a previous history of T-cell lymphoma elsewhere (the mean delay between systemic and ocular involvement being 6 years). The predominant primary site was cutaneous, particularly of the mycosis fungoides type. Therapy choice and prognosis depend partly on immunocytochemical classification but prognosis is often poor.

Peripheral T-cell lymphomas constitute over 10% of non-Hodgkin's lymphomas and are clinically and histologically diverse. Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL) is now separately listed in the WHO 2008 classification of lymphomas⁵ with two distinct anatomic subtypes: hepatosplenic and cutaneous. About 95% of normal T-cells express the alpha-beta dimer form of T-cell receptor, whereas 5% express gamma-delta. These cells are cytotoxic, have some regulatory function and normally lack both CD4 and CD8.⁶ Malignancies of the gamma-delta cell are rare; only 2 of 62 cutaneous T-cell lymphomas bore this marker.⁷ Mortality is higher in PCGDTCL than in other cutaneous T-cell lymphomas.⁸ Involvement of the CNS is very rare, only five published cases being identified by

a recent review.⁹ Ocular adnexal involvement by PCGDTCL causing proptosis has been reported,^{10 11} but intraocular involvement has been reported in only one patient with bilateral non-granulomatous anterior uveitis.¹¹ Involvement of the retina or ocular posterior segment has never previously been reported.

There are some discrepancies between skin histology and vitreous cytology in this case. The immunohistochemistry panel on the (much smaller) vitreous sample was narrower than that performed on skin to save material for PCR for diagnostic confirmation. The main difference was CD8 positivity in vitreous and negativity in skin. This, however, does not exclude the diagnosis as CD8-positive gamma-delta T-cell lymphoma has also been described.

Contributors All authors were involved in the clinical care of the patient. NJ conceived the case report. The manuscript was drafted by NJ and contributed to by all authors. Data on histology and cytology was provided by LI and SC. All authors performed a literature search and contributed references. All authors read and corrected the draft manuscript. NJ sourced the clinical images. LI sourced the cytology images.

Competing interests None declared.

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Learning points

- Patients presenting with synchronous ocular and skin lesions should be investigated for systemic infection and malignancy.
- Almost all lymphomas involving vitreous and retina are of B-cell origin. Intraocular T-cell lymphoma is extremely rare.
- Early multidisciplinary input is key to rapid diagnosis and optimising patient outcomes.
- The CODOX-M/IVAC polychemotherapy regimen is the current standard for high-grade non-Hodgkin's lymphomas involving central nervous system but may not provide long-term resolution.

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