BMJ Case Reports

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

Journal:	*BMJ Case Reports*
Manuscript ID	bcr-2017-219946
Manuscript Type:	Rare disease
Date Submitted by the Author:	23-Feb-2017
Complete List of Authors:	Jones, Nicholas; Manchester Royal Eye Hospital, Gibb, Adam; Christie NHS Foundation Trust Irion, Luciane; Manchester Royal Eye Hospital Coupland, Sarah; University of Liverpool
Keywords:	Skin cancer < Oncology, CNS cancer < Oncology, Retina < Ophthalmology

BMJ Case Reports

Submission template for full cases

- All case reports MUST be submitted online using this Word template http://mc.manuscriptcentral.com/bmjcasereports
    - You will be asked for more detailed information on submission where you can also upload images, multimedia files, etc
    - Further details are available in the Instructions for authors http://casereports.bmj.com/instructions-for-authors
- You must have **signed informed consent** from patients (or relatives/guardians) before submitting to BMJ Case Reports. Please anonymise the patient's details as much as possible, eg, specific ages, occupations. Consent forms are available in several languages http://casereports.bmj.com/instructions-for-authors/consentform.pdf
- You or your institution must be a Fellow of BMJ Case Reports in order to submit. Fellows can submit as many cases as they like, access all the published material, and re-use any published material for personal use and teaching without further permission.
    - For more information on rates and how to purchase your fellowship visit http://casereports.bmj.com/misc/becomeafellow.dtl
    - Contact your librarian or head of department to see if your institution already has a Fellowship

TITLE OF CASE

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

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

A young man presented with rapid, predominantly right-sided visual loss with a background of multifocal skin lesions. He showed panuveitis with bilateral multifocal retinal infiltrates and retinal vasculitis and visual acuity (VA) of Hand Movements. 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 right VA to 6/7.5 but 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.

BACKGROUND ***Why you think this case is important – why did you write it up?***

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 ***Presenting features, medical/social/family history***

A 41 year-old Caucasian man presented with rapidly deteriorating vision in both eyes over 5 days. 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 peri-arteriolar), and retinal arteriolitis (Figure 1). The left eye showed fewer, better-defined white retinal deposits (Figure 2). He was also noted to have multiple violaceous placoid skin lesions (Figure 3). The itchy but painless skin

lesions had been spreading and enlarging for several months and the largest, on the left buttock, was 5cmx2cm and apparently necrotising (Figure 4). 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 Valciclovir 1 gm TDS, Doxycycline 100mg BD and Penicillin V 500 mg QID.

INVESTIGATIONS ***If relevant***

Investigations revealed a normal full blood count, normal liver function, an elevated creatinine to 120 µmol/l), C-reactive protein (<1), angiotensin converting enzyme 43 IU/l, no autoantibodies, slightly raised IgA (3.22g/l) with no paraprotein bands, normal chest X-ray, negative serology for syphilis, Aspergillus, Streptococcus, Borrelia, Herpes simplex (HSV) I + II, Human immunodeficiency virus I + II, Human T-lymphotrophic virus I + II and Rickettsia. Varicella-zoster (VZV) IgG (but not IgM) was detected and polymerase chain reaction (PCR) testing was negative for VZV, HSV I + II, Cytomegalovirus and Pneumocystis.

Magnetic resonance imaging 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 (Fig 5a,b). Whole-body computed tomography 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 (Fig 6). There were numerous cells undergoing apoptosis. Immunohistochemistry demonstrated that the atypical cells were positive for T-cell markers (CD2, CD3 (Fig 5), CD8>CD4 and CD79a) but CD5 was negative as were CD10, CD23 and CD30. There was focal positivity for CD56, and the Ki-67 growth 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.

The patient also underwent incisional biopsy of the largest skin lesion, histology showing nested aggregates of atypical lymphocytes with prominent 'tagging' of these cells along the basal epidermis. In the deeper dermis, infiltrates were predominantly perivascular, without angio-invasion. Immunohistochemistry showed cells positive for CD2, CD3, CD45, CD56, TIA-1, granzyme B and S-100P; CD4, CD5, CD8 and CD20 were negative, and there was virtually complete loss of CD7. These features confirmed T-cell lymphoma of gamma-delta type, involving skin, eye and brain, a diagnosis confirmed at a supra-regional lymphoma multidisciplinary meeting.

DIFFERENTIAL DIAGNOSIS ***If relevant***

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

TREATMENT ***If relevant***

The patient was commenced on the CODOX-M/IVAC polychemotherapy regimen (intravenous cyclophosphamise, doxorubicin, vincristine, high-dose methotrexate, alternating with ifosfamide, cytarabine and etoposide alongside intrathecal methotrexate and cytarabine), originally devised for Burkitt lymphoma but also utilised for high-grade non-Hodgkin lymphoma involving the 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.

OUTCOME AND FOLLOW-UP

Retinal infiltration and intraocular involvement resolved rapidly on treatment and within 3 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 (Fig 7). The cutaneous plaques and necrotic buttock lesion resolved completely. Systemic re-staging via FDG-PET-CT and MRI brain revealed a complete metabolic and radiologic response. Unfortunately whilst awaiting consolidating syngeneic haemopoetic stem cell transplant (the patient has a twin brother), he underwent clinico-radiological 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. Palliative care was organised.

DISCUSSION ***Include a very brief review of similar published cases***

Intraocular lymphoma may be secondary to systemic lymphoma (in which cases lesions are usually discrete and choroidal) or may arise primarily within the eye (primary vitreoretinal lymphoma [PVRL], part of a presumed multicentric primary CNS and vitreoretinal malignancy). Intraocular lymphoma is increasing in incidence, but almost all cases are PVRL of large B-cell origin[1]. Primary vitreoretinal lymphoma of T-cell type is exceedingly rare 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 eye[4] 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 upon immunocytochemical classification but prognosis is often poor.

Peripheral T-cell lymphomas constitute over 10% of non-Hodgkin lymphomas and are clinically and histologically diverse. Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL) is now separately listed in the World Health Organisation 2008 classification of lymphomas[5] with two distinct anatomic subtypes: hepatosplenic and cutaneous. About 95% of normal T-cells express the αβ dimer form of T-cell receptor, whereas 5% express γδ. These cells are cytotoxic, have some regulatory function and normally lack both CD4 and CD8[6]. Malignancies of the γδ 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 central nervous system is very rare, only 5 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.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

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 lymphomas involving CNS, but may not provide long-term resolution

REFERENCES ***Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)***

References:

1. Chan CC, Rubenstein JL, Coupland SE, Davis JL, Harbour JW, Johnston PB, Cassoux N, Touitou V, Smith JR, Batchelor TT, Pulido JS. Primary vitreoretinal lymphoma: A report from an International Primary Central Nervous System Lymphoma Collaborative Group Symposium. Oncologist. 2011;16(11):1589-99. Epub 2011 Nov 1

2. Coupland SE, G Anastassiou, N Bornfeld, M Hummel, H Stein. Primary Intraocular T-cell Lymphoma: Report of a case and review of the literature. Graefes Arch Clin Exp Ophthalmol. 2005; Mar;243(3):189-97

3. Chaput F, Amer R, Baglivo E, Touitou V, Kozyreff A, Bron D et al. Intraocular T-cell lymphoma: clinical presentation, diagnosis, treatment, and outcome. Ocul Immunol Inflamm 2016;Epub

4. Levy-Clarke G, Greenman D, Sieving PC, Byrnes G, Nussenblatt R, Chan C-C. Ophthalmic manifestations, cytology, immunohistochemistry and molecular analysis of intraocular metastatic T-cell lymphoma: report of a case and review of the literature. Surv Ophthalmol 2008;53:285-95

5. O'Leary HM, Savage KJ. Update on the World Health Organization classification of peripheral T-cell lymphomas. Curr Hematol Malig Rep 2009;4:227–235

6. Bluestone JA, Khattri R, Sciammas R, Sperling AI. TCR gamma delta cells: a specialized T-cell subset in the immune system. Ann Rev Cell Dev Biol 1995;11:307–353

7. Ralfkiaier E, Wolf-Sneedorff A, Thomsen K, Geisler C, Vejlsgaard GL. T-cell receptor gamma-delta positive peripheral T-cell lymphomas presenting in the skin: a clinical, histological and immunophenotypic study. Exp Dermatol 1992;1:31-38

8. Toro JR, Liewehr DJ, Pabby N, Sorbara L, Raffeld M, Steinberg SM et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood 2003;101:3407-12

9. Harrington L, Sokol L, Holdener S, Dhao H, Zhang L. Cutaneous gamma-delta T-cell lymphoma with central nervous system involvement: report of a rarity with review of the literature. J Cutan Pathol 2014;41:936-43

10. Sugnanam K, Ooi L, Mollee P, Vu P. Gamma-delta T-cell lymphoma with CNS involvement presenting with proptosis: a case study workup, treatment and prognosis. Orbit. 2012;31:364-6

11. Shunmugam M, Chan E, O'Brart D, Moonim MT, Stanford MR, Morley AM. Cutaneous γδ T-cell lymphoma with bilateral ocular and adnexal involvement. Arch Ophthalmol 2011;129:1379-81

FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

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

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

Figure 3 One of several groups of itchy but painless violaceous skin lesions, this one on the thigh

Figure 4 The largest skin lesion, on the left buttock, measured 5cmx2cm and showed central crusting

Figure 5 Horizontal (a) and coronal (b) T2-weighted MRI scans at presentation showing infiltration of left cerebral peduncle and internal capsule

Figure 6 Vitrectomy sample showing atypical lymphocytes with pleomorphic nuclei, some with prominent nucleoli, and numerous apoptotic bodies.

Figure 7 The right fundus after first-phase chemotherapy, three weeks after presentation, showing complete resolution of vasculitis, virtual elimination of retinal infiltration and widespread retinal pigment epithelial atrophy. Visual acuity: 6/7.5

Copyright Statement

Date:23/02/2017

PLEASE SAVE YOUR TEMPLATE WITH THE FOLLOWING FORMAT:

Corresponding author's last name and date of submission, eg,

Smith_May_2009.doc

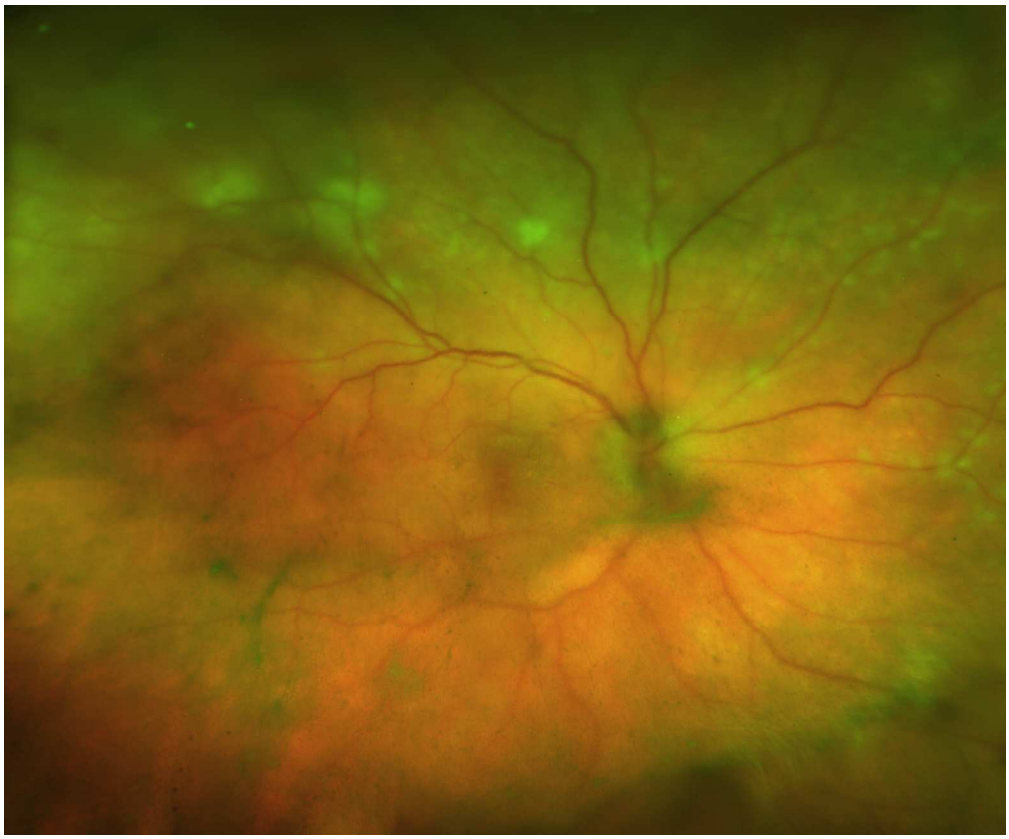

Figure 1 The right fundus at presentation showing severe vitritis with widespread multifocal retinal infiltrations of variable size, particularly perivascular. Visual acuity: Hand Movements

449x372mm (150 x 150 DPI)

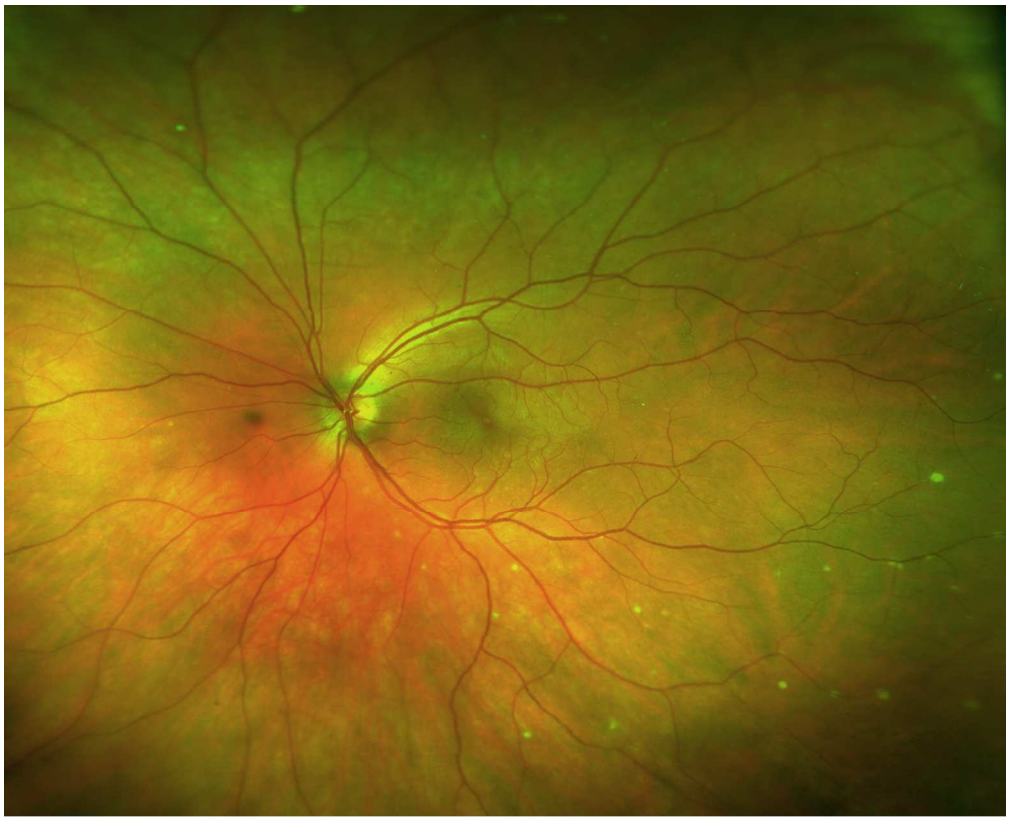

Figure 2 The left fundus at presentation, with no vitritis but multifocal small well-defined retinal infiltrates

473x384mm (150 x 150 DPI)

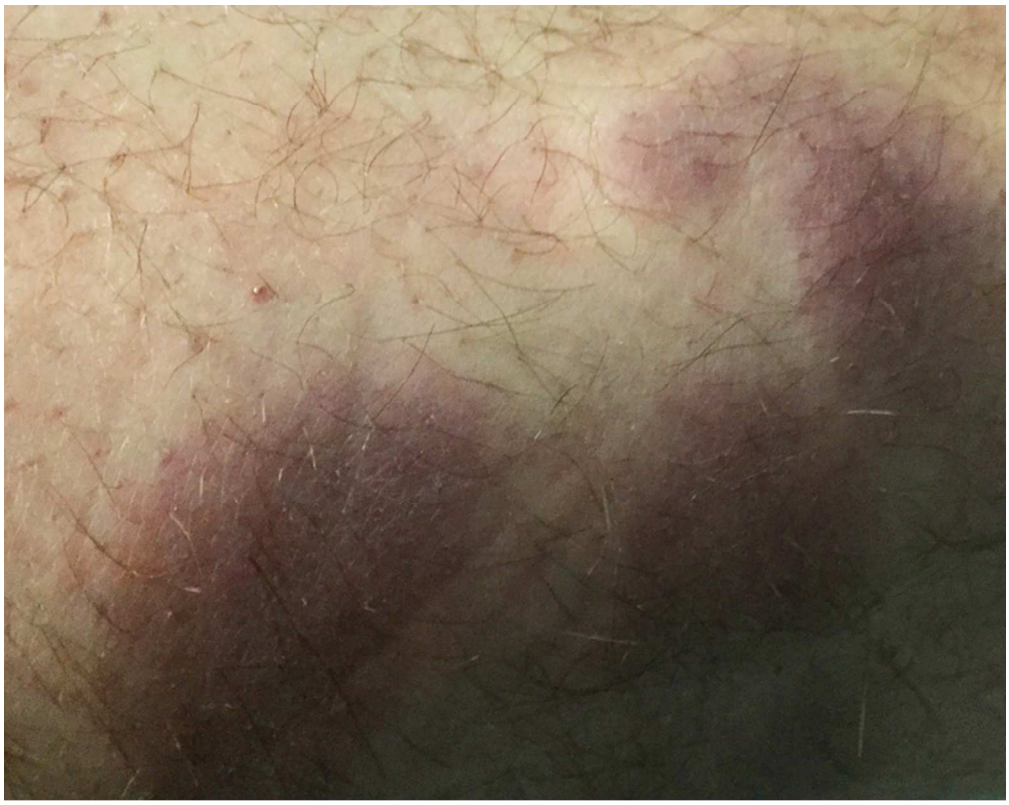

Figure 3 One of several groups of itchy but painless violaceous skin lesions, this one on the thigh

146x116mm (150 x 150 DPI)

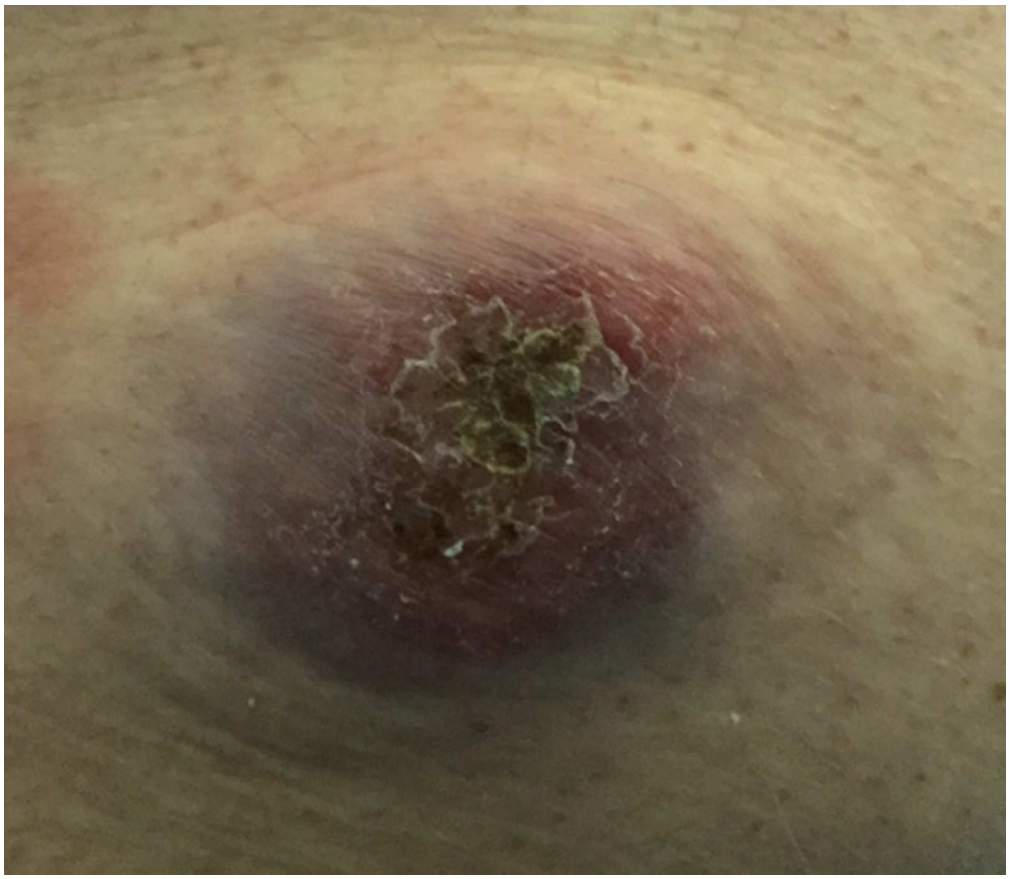

Figure 4 The largest skin lesion, on the left buttock, measured 5cmx2cm and showed central crusting

99x86mm (150 x 150 DPI)

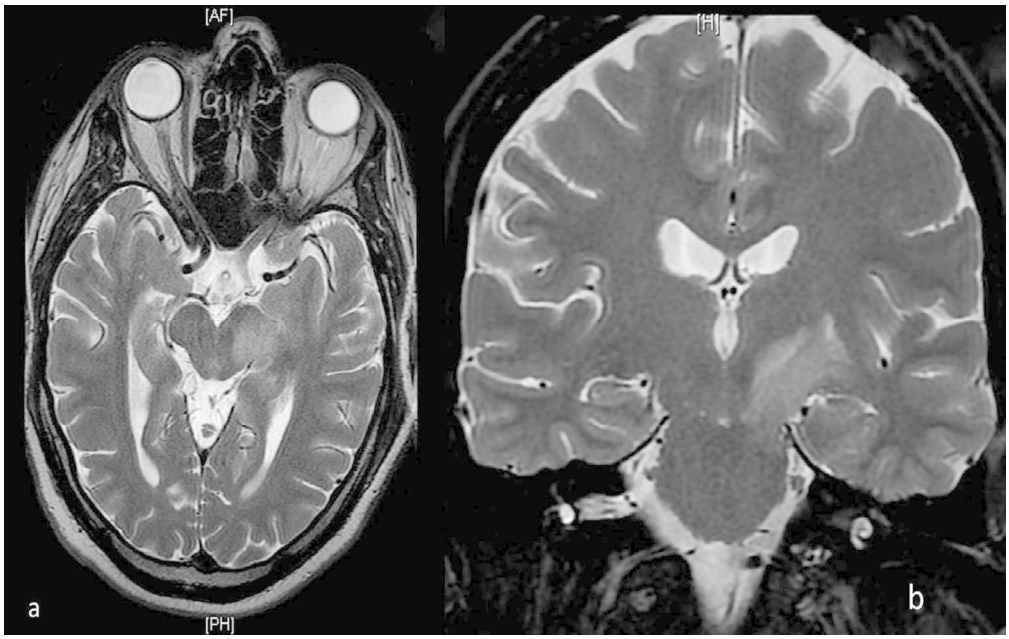

Figure 5 Horizontal (a) and coronal (b) T2-weighted MRI scans at presentation showing infiltration of left cerebral peduncle and internal capsule

254x159mm (150 x 150 DPI)

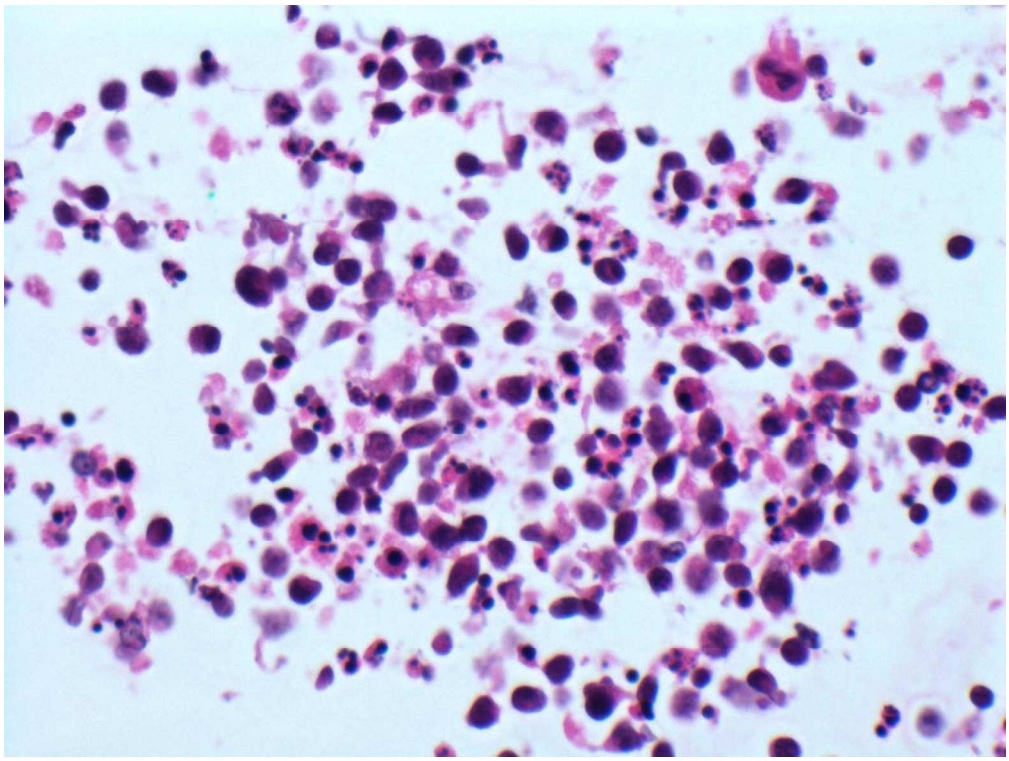

Figure 6 Vitrectomy sample showing atypical lymphocytes with pleomorphic nuclei, some with prominent nucleoli, and numerous apoptotic bodies.

218x163mm (150 x 150 DPI)

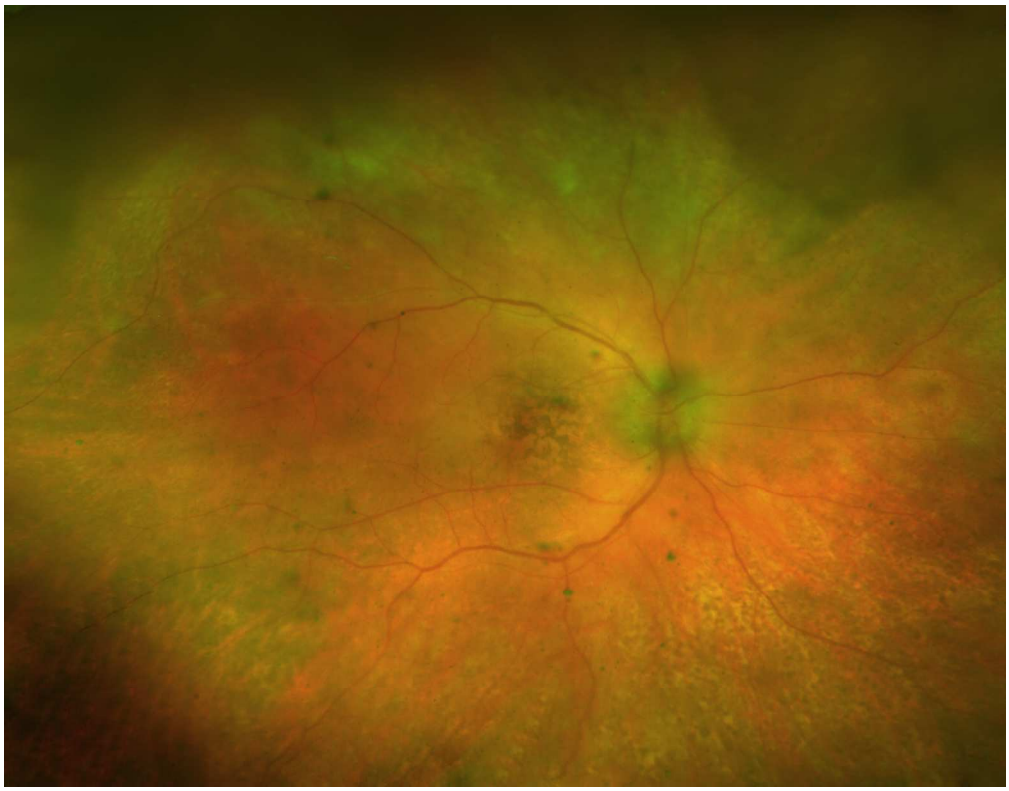

Figure 7 The right fundus after first-phase chemotherapy, three weeks after presentation, showing complete resolution of vasculitis, virtual elimination of retinal infiltration and widespread retinal pigment epithelial atrophy. Visual acuity: 6/7.5

454x354mm (150 x 150 DPI)