

CASE REPORT**Intravascular lymphomatosis****P C W Lui, G K C Wong, W S Poon, G M K Tse***J Clin Pathol* 2003;**56**:468–470

Intravascular lymphomatosis (IVL) is a rare angiotrophic large cell lymphoma producing vascular occlusion of arterioles, capillaries, and venules. Antigenic phenotyping shows that these lymphomas are mostly of B cell type, and less commonly T cell or Ki-1 lymphomas. The central nervous system and skin are the two most commonly affected organs; patients usually present with progressive encephalopathy with mental status changes and focal neurological deficits and skin petechia, purpura, plaques, and discolouration. Other involved organs include adrenal glands, lungs, heart, spleen, liver, pancreas, genital tract, and kidneys. Bone marrow, blood, cerebrospinal fluid, and lymph nodes are typically spared. Fever of unknown origin is another common presentation. Only one case of IVL presenting with disseminated intravascular coagulation and anasarca (generalised oedema) has been reported in the literature. This report describes a postmortem case of a patient with IVL who initially presented with disseminated intravascular coagulation complicated by intracerebral haemorrhage.

Here, we report an extremely rare postmortem case of a patient with intravascular lymphomatosis (IVL) who initially presented with disseminated intravascular coagulation (DIC) complicated by intracerebral haemorrhage.

CASE REPORT

A 41 year old woman presented with acute onset of blurred vision in the left eye with a dilated and non-reactive pupil and almost total gaze palsy sparing only the upward gaze. Magnetic resonance imaging of the brain showed left optic nerve inflammation and diffuse thickening. The preliminary diagnosis was

Tolosa Hunt syndrome, characterised by unilateral ophthalmoplegia with orbital pain and pain in the area supplied by the first division of the trigeminal cranial nerve. This was thought to be caused by non-specific inflammation and granulation tissue formation in the superior orbital fissure or cavernous sinus. Steroid treatment was started and her condition improved. Three months later, after tailing down the dose of the prednisolone for two weeks, she complained of severe pain and lateral gaze palsy of the left eye. Her condition deteriorated rapidly and she became comatose. Lumbar puncture showed normal opening pressure, and there was no evidence of infection. She developed acute renal and liver failure with disseminated intravascular coagulopathy requiring repeated platelet transfusion. Viral serology, bronchioloalveolar lavage, and cultures were negative. She was treated for presumed sepsis, and a subsequent interval computed tomography brain scan showed diffuse spotty subcortical haemorrhages. She died a few weeks later from multiorgan failure and sepsis. Postmortem examination revealed evidence of DIC, with multiple petechial haemorrhages over mucous membrane, pleura, and pericardium, and with fibrin deposition in the kidney. Multiple areas of haemorrhage were noted in the brain. Within the blood vessels in the leptomeninges, around the optic nerves, lungs, kidneys, thyroid, and liver, an atypical lymphoid cell population was noted (fig 1). The cells possessed large nuclei and prominent nucleoli. They expressed leucocyte common antigen (LCA) and CD20, (fig 2) but not CD3 or Ki-1. A diagnosis of intravascular lymphomatosis was rendered.

Abbreviations: DIC, disseminated intravascular coagulation; IVL, intravascular lymphomatosis; LCA, leucocyte common antigen

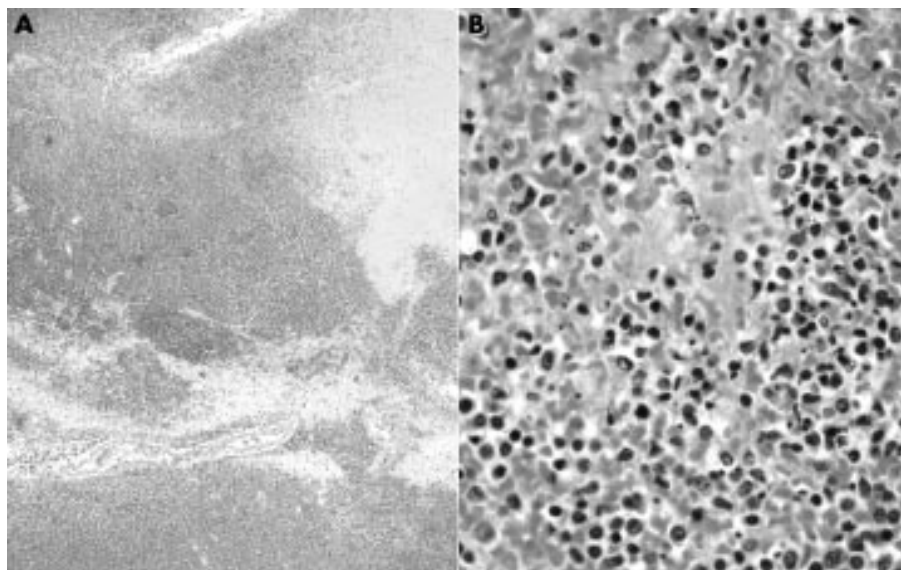


Figure 1 Photomicrographs showing (A) areas of haemorrhagic infarcts within the cerebral cortex, and (B) the presence of atypical lymphoid cells within the infarcts.

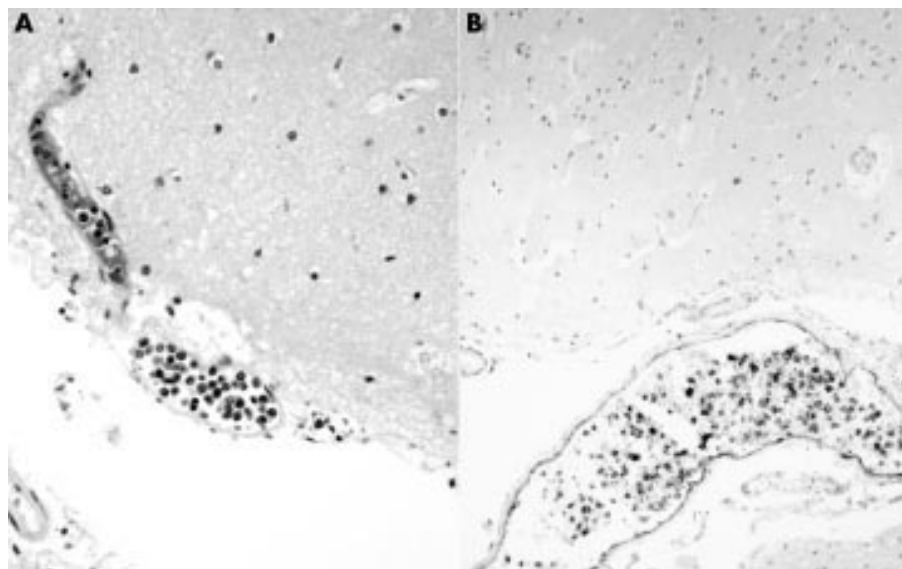


Figure 2 Photomicrographs showing (A) lymphoma cells within the surface small vessels over the cerebral cortex, and (B) that the cells are CD20 positive.

DISCUSSION

IVL is a rare intravascular subtype of extranodal large cell lymphoma featuring multifocal vascular occlusion, and resulting in diffuse thrombosis, a high incidence of neurological and cutaneous involvement, a poor response to chemo/radiotherapy, and an extremely aggressive clinical course. The mechanism for the intravascular growth pattern has not been defined, and a lack of homing receptors and adhesion molecules including CD29 (β 1 integrin) and CD54 (intercellular adhesion molecule 1) has been hypothesised.^{1,2} Although many organs can be affected by IVL, the vasculature within the brain and skin are especially susceptible. This organ susceptibility phenomenon is another unexplained issue. It seems that the endothelial cells of certain organs have a high affinity of binding to the lymphoma cells that have a defect in adhesion molecules. The affected blood vessels show reactive endothelial cells adjacent to lymphoma cells, and complete occlusion of vessel lumina can be seen.³ Endothelial markers such as CD31 may help to distinguish them from the lesional cells in difficult cases.

“The mechanism for the intravascular growth pattern has not been defined, and a lack of homing receptors and adhesion molecules including CD29 (β 1 integrin) and CD54 (intercellular adhesion molecule 1) has been hypothesised”

In our case, the patient presented with DIC, which was later complicated by intracerebral haemorrhage. DIC is a thrombohaemorrhagic disorder characterised by formation of

microthrombi throughout the microcirculation with consumption of platelets, fibrin, and coagulation factors. At the same time, the fibrinolytic pathway is activated, leading to haemorrhagic diathesis. In the past, only one case of IVL presenting as DIC and anasarca has been reported.⁴ This rare presentation may mislead the clinician into considering more common clinical disease entities, leading to a delay in diagnosis or even a missed diagnosis. Blood tests for platelet count, prothrombin time, activated partial thromboplastin time, and D dimer confirm the presence of DIC. Biopsy of the affected organ tissue with particular attention to the small vessels leads to the correct diagnosis in these cases.

The pathogenesis of DIC in IVL is poorly understood. Stahl proposed that the combination of vessel obstruction by lymphoma cells and tumour embolisation is necessary to induce DIC in IVL.⁴ The secretion of procoagulants by the tumour may lead to consumptive coagulopathy. Direct interaction between the lymphoma cells and the endothelial cells, resulting in endothelial cell damage and subsequently tissue factor release, may also be possible.

The localised manifestation of intracerebral haemorrhage in the background of DIC is unreported. The presence of lymphoma cells within the vessels may distort the haemostatic balance of the vascular endothelium, thus triggering haemorrhage.^{5,6}

The differential diagnoses of intravascular malignancy include metastatic carcinoma, angiocentric lymphoma, sarcoma, lymphocytic leukaemia, metastatic melanoma, and IVL. In most instances, there is evidence of primary origin of the tumour. Morphological assessment is usually sufficient for confident differentiation. However, in difficult cases, a panel of immunohistochemical antibodies should be used, including those directed at LCA, cytokeratin, vimentin, HMB45, CD56, and CD5.

There is no effective treatment for IVL: these tumours are not responsive to chemotherapy⁷ or radiotherapy.³ The median survival after onset of symptoms has been reported to be four months, with a range of one day to 44 months.³ Increasing awareness of this disease as a differential diagnosis to a common clinical presentation may lead to more opportunities to evaluate new treatment approaches.

Take home messages

- This is only the second case of intravascular lymphomatosis initially presenting with disseminated intravascular coagulation complicated by intracerebral haemorrhage to be reported in the literature
- There is no effective treatment for these tumours because they are not responsive to chemotherapy or radiotherapy
- Increasing awareness of this disease as a differential diagnosis to a common clinical presentation may lead to more opportunities to evaluate new treatment approaches

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ECHO

PCR analysis of aqueous humour reliably identifies causal pathogens in necrotising retinitis



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Patients with necrotising herpetic retinitis stand a chance of better management with the finding that PCR analysis of aqueous humour can reliably identify the causal pathogen.

The method detected viral DNA in 86% of patients (19/22, 23 eyes) with acute retinal necrosis (ARN) and specifically identified herpes simplex virus (HSV) 1 (two patients) and 2 (four), varicella zoster virus (VZV) (six) and cytomegalovirus (CMV) (four). Three patients with progressive outer retinal necrosis (PORN) all had samples positive for VZV. Among five negative samples, two were positive with repeat samples and in the others antiviral treatment had started before sampling. Samples from controls were all negative for viral DNA.

The investigators recruited 22 patients (29 eyes) with ARN diagnosed according to American Uveitis Society criteria or with PORN. Ten patients with active, non-viral uveitis were the controls. Between 100–150 µl aqueous humour was aspirated from the eyes during an anterior chamber tap on the day of admission. Samples from 22 patients were used in a single PCR to detect herpesvirus DNA and to identify HSV-1, HSV-2, and Epstein-Barr virus (EBV) by restriction analysis of PCR products. Separate assays were performed for CMV and VZV.

Necrotising herpetic retinitis is a condition covering ARN and PORN caused by HSV-1, HSV-2, VZV, CMV, or EBV. Diagnosis is usually clinical but can be uncertain, causing delay in starting the most suitable treatment. Previous work on the diagnostic value of PCR focused on vitreous humour. However, collecting aqueous humour is an easier and safer procedure.

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