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# An autopsy case report of sudden collapse: Diffuse large B cell lymphoma with predominant intravascular distribution and bone marrow involvement

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## ABSTRACT

**Introduction:** Diffuse large B cell lymphoma is a type of high grade B cell lymphoma. There is one variant named as intravascular large B cell lymphoma (IVLBCL), which is an uncommon entity with high mortality rate. The diagnosis could be difficult as the clinical presentation could be subtle and sometimes a post-mortem diagnosis. The latter variant can show bone marrow involvement, especially in Asian cases.

**Case Report:** We report a case of diffuse large B cell lymphoma with predominant intravascular distribution presenting as sudden death. The diagnosis was made by histology examination of the tissue at various parts of body. Subsequent immunohistochemical studies confirmed the presence of lymphoma cells inside blood vessels. Bone marrow involvement is noted.

**Conclusion:** This case should raise the alertness of malignant lymphoma cells inside blood vessels during autopsy. Awareness of such entity during ante-mortem biopsy and autopsy helps to delineate the cause of clinical deterioration.

**Keywords:** Diffuse large B cell lymphoma, Intravascular large B cell lymphoma, Sudden death

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## INTRODUCTION

Diffuse large B cell lymphoma is the commonest type of malignant lymphoma. One of the rare variants is intravascular large B cell lymphoma (IVLBCL). Intravascular large B cell lymphoma is characterized by the preferential intravascular growth of lymphoma cells within the lumen of small blood vessels, particularly capillaries. It has an aggressive behavior, and is often fatal [1, 2]. By definition, the diagnosis of IVLBCL is made by selective growth of neoplastic cells within the lumina of small and medium-sized blood vessels of several organs. Central nervous system (CNS) is often involved in such cases.

The WHO 2017 version defines that IVLBCL is a type of extranodal large B cell lymphoma which has “selective growth within the lumina of blood vessels, particularly capillaries, with the exception of larger arteries and veins.” Among the cases of IVLBCL, the lymphoma cells can also show wide dissemination in extranodal sites. Bone marrow is a common site of involvement. Other organs may have extravascular component. However, the lymph nodes are usually spared.

There is no specific clinical sign or symptom for IVLBCL. Non-specific symptoms including fever, loss of appetite, and fatigue may occur as the only symptoms.

Neurological signs or symptoms are often present, yet non-localizing. No definite nodular tumor is formed, rending diagnosis difficult.

We here report an autopsy case findings of a diffuse large B cell lymphoma, with predominant intravascular distribution, together with extravascular involvement by malignant cells in multiple organs and bone marrow.

## CASE REPORT

A 73-year-old man was referred to our department for an autopsy due to sudden collapse in medical ward with uncertain cause of death. This man was clinically admitted into medical ward due to pancytopenia and atypical cells in peripheral blood smear.

His past medical history was retrieved via the patient information network (ePR). Five months before admission, he was diagnosed to be suffering from pulmonary tuberculosis and received Rifampicin, Isoniazid, and Pyrazinamide. He had no history of immunosuppression or other signs of being immunocompromised. His baseline blood count was normal.

One month ago, he complained loss of appetite and tiredness during medical follow-up. On examination, there was no significant lymphadenopathy. The complete blood count showed reduced in white cell count and neutrophil count (white cell reduced from $8.1\times10^9$/L to $3.0\times10^9$/L, neutrophil count dropped from $5.2\times10^9$/L to $0.2\times10^9$/L). His platelet count was low ($14\times10^9$/L). His hemoglobin level dropped from 15.1 to 12.8 g/dL. He was initially impressed to be suffering from drug induced thrombocytopenia related to the anti-tuberculosis drug he was using at the moment. Some investigations, including peripheral blood smear, chest X-ray, and abdominal X-rays were performed in the outpatient setting.

Peripheral blood smear revealed medium to large-sized atypical lymphocytes with oval to slightly irregular nuclei, open chromatin, deeply basophilic cytoplasm, and some with cytoplasmic granulations.

Repeated chest and abdominal X-rays showed no significant mass or tumor. Therefore, he was arranged to be admitted clinically into medical ward for more investigations.

On the day of admission, he was asymptomatic with stable vitals, with a clinical impression of anti-tuberculosis medications related thrombocytopenia. He developed low grade fever after admission. Chest X-ray showed right lower zone consolidation shown in chest X-ray. He received antibiotics treatment. Two days after admission, he developed sudden cardiac arrest. Resuscitation was failed and he succumbed. Para-mortem blood picture showed disseminated intravascular coagulopathy. His death was referred for autopsy in view of uncertain cause of death.

## Autopsy and pathological findings

The patient was of medium body built. There was no lymphadenopathy at external examination. The skin showed no rash or bullous formation.

During autopsy, both lungs were heavy with the right lung weighing 777 grams and left lung weighing 834 grams. The organs, otherwise, showed no gross lesion. There was no significant lymphadenopathy at cervical, groin, intrathoracic, or intra-abdominal cavity. On sectioning, the lung parenchyma was congested and both lungs showed several small white calcified nodules, of which the largest measured 3 mm in diameter, compatible with previous known tuberculosis. Otherwise, other organs show no gross abnormalities. Pulmonary trunks showed no large thrombi. The deep vein at the lower limbs showed no significant thrombi as well. Tissue sample blocks were taken among various internal organs.

On microscopic examination, infiltrates of large lymphoma cells are note in the vascular spaces of meninges, brain, spleen, pericardium, myocardium, both lungs, both adrenal glands, both kidneys, lymph nodes, salivary gland, and bone marrow (Figures 1–4). The neoplastic lymphoid cells bear large nuclei and prominent nucleoli with frequent mitotic figures. Immunohistochemically, they are positive for CD20 and CD79a, while negative for CD3 (Figures 5 and 6). They exhibit Ki 67 proliferative index at 99% (Figure 7). CD5, MUM1 are negative (Figure 8).

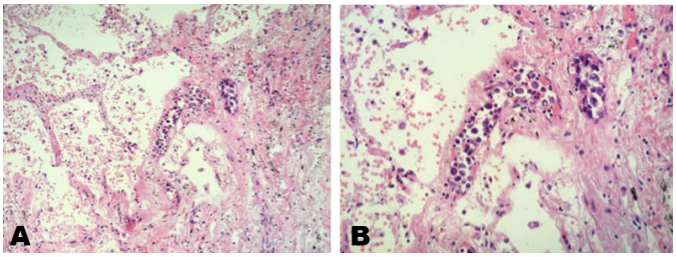


Figure 1: Lung at (A) 200× and (B) 400× magnification, respectively, showing aggregates of neoplastic lymphoid cells of similar morphology.

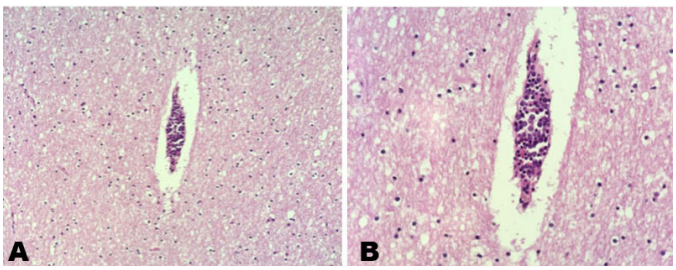


Figure 2: Brain at (A) 200× and (B) 400× magnification, respectively, showing aggregates of neoplastic lymphoid cells of similar morphology.

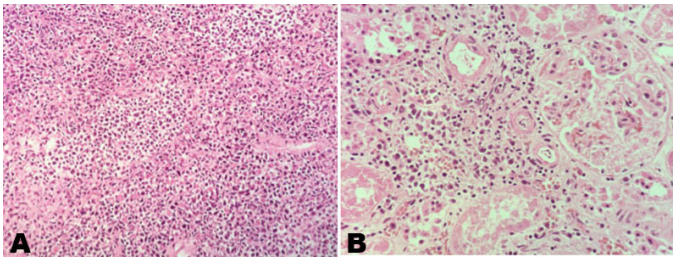


Figure 3: (A) Adrenal gland at 200× magnification and (B) kidney at 400× magnification, respectively, showing aggregates of neoplastic lymphoid cells of similar morphology.

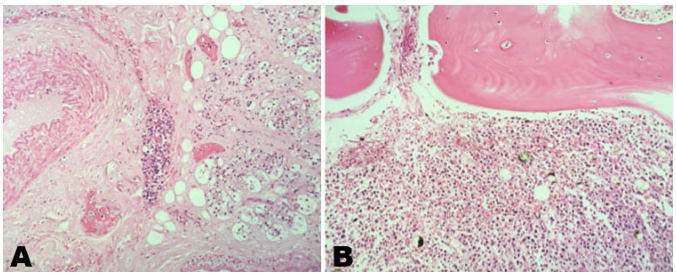


Figure 4: (A) Salivary gland at 200× magnification and (B) bone marrow and 200× magnification, respectively, showing aggregates of neoplastic lymphoid cells of similar morphology.

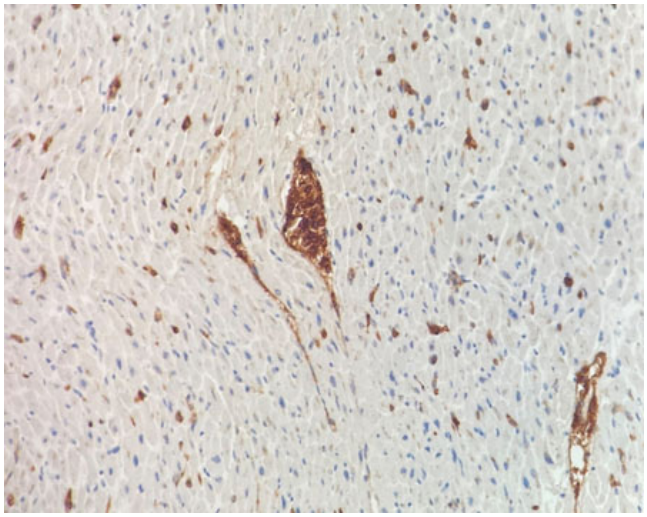

Figure 5: Immunostain CD20 at 200× magnification showing the lymphoma cells are positive for CD20.

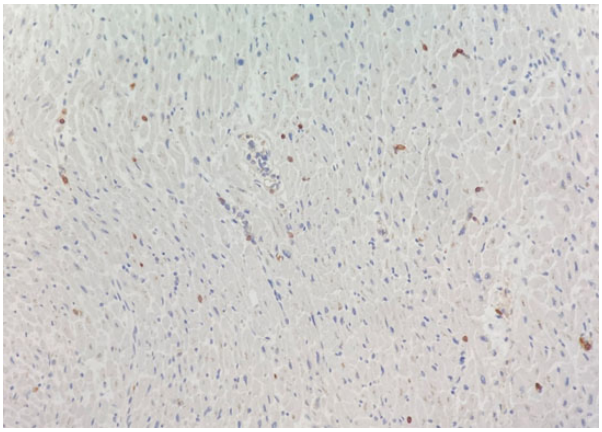

Figure 6: Immunostain CD3 at 200× magnification showing the lymphoma cells are negative for CD3.

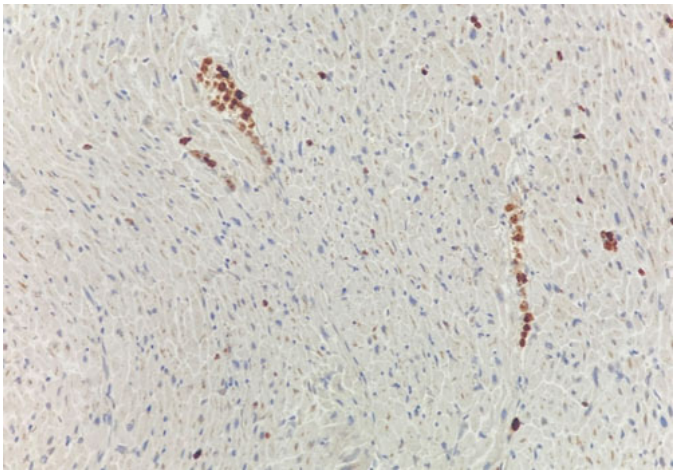

Figure 7: Immunostain for Ki67 at 200× magnification. The lymphoma cells have a very high proliferative index, at 99%.

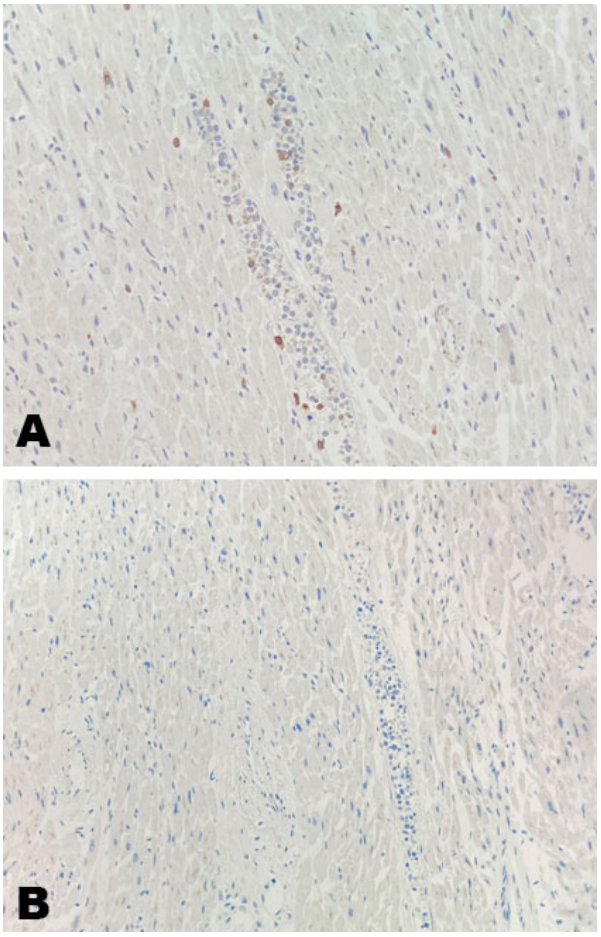


Figure 8: Immunostain for (A) CD5 and (B) MUM-1 at 200× magnification. Both are negative among the intravascular tumor cells.

## DISCUSSION

Intravascular large B cell lymphoma is defined as an extranodal large B cell lymphoma characterized by the selective growth of lymphoma cells within the lumen of vessels, in particular capillaries, with the exception of

larger arteries and veins [1]. It is challenging to diagnose in ante-mortem situation. Having a high index of suspicion, biopsies of various organs, early institution of treatment should be considered. This case is considered to be a classic subtype, given no features of hemophagocytic syndrome.

Laboratory findings may include anemia, thrombocytopenia, liver, and renal impairment [1]. The clinical presentation of IVLBCL can be bewildering, usually related to the occlusion of small vessels. The clinical features are non-specific, including non-localizing signs of fever, loss of appetite, skin lesions [2, 3]. Neurologic signs are often misleading, which may present as dementia, stroke, or peripheral neuropathy [4, 5]. In our case, the clinical presentation was complicated by the differential diagnosis of drug induced thrombocytopenia, as initially thought the abnormal blood picture was a result of anti-tuberculosis drug.

Intravascular large B cell lymphoma usually occurs in the elderly patient, with a median age of 67 [6–8]. Organ biopsies are mandatory for the diagnosis of IVLBCL. As IVLBCL can involve any organs, the organs selected by the physician for biopsy are key to accurate diagnosis [9, 10]. Marrow involvement can be seen as well. In an Asian study, the most relevant diagnostic site was the bone marrow [11]. Unfortunately in this case, ante-mortem bone marrow examination was not available.

The cause of death in a case of intravascular lymphoma can be multifactorial [12, 13]. Diffuse thrombosis with a high incidence of neurological involvement can cause sudden death. The mechanism for the intravascular growth pattern has not been defined, and a lack of homing receptors and adhesion molecules including CD29 (β1 integrin) and CD54 (intercellular adhesion molecule 1) has been hypothesized [14].

The thrombotic even among the small vessels can result in disseminated intravascular coagulopathy (DIC). Some author suggests that DIC was induced by small vessel obstruction by malignant lymphoma cells. Such small vessel events of obstruction can induce DIC and is irreversible. The lymphoma cells may also directly damage the blood vessel walls and induce the secretion of coagulative factors [15, 16].

Other differential diagnosis of intravascular lymphoma should include diffuse large B cell lymphoma with dissemination. In our case, the lymphoma cells are mainly in the intravascular cavity, rendering such differential diagnosis less likely. Metastatic carcinoma should also be considered in histological sections. Immunohistochemical staining can easily differentiated from lymphoma. In uncertain cases, more immunostains including melanocytic markers (HMB45, S100, SOX-10), epithelial markers (CK, AE1/3, CAM5.2) can be used for a wider range of differential diagnosis [17].

## CONCLUSION

For a case of diffuse large B cell lymphoma with predominantly intravascular component, extravascular involvement of lymphoma cell does not exclude IVLBCL. We would recommend a comprehensive analysis to characterize and find differences between the intravascular and extravascular components. Clinicians should be aware of such entity of IVLBCL. Timely investigations, including bone marrow examination, may shorten the time to arrive the diagnosis, therefore can formulate more focused treatment depending on each patient's unique presentation. The increase in awareness of such differential diagnosis among clinicians may lead to more evaluation for new treatments in such entity.

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## Author Contributions

Chun-hai LO – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Shui-ying CHENG – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

## Guarantor of Submission

The corresponding author is the guarantor of submission.

## Source of Support

None.

## Consent Statement

Written informed consent was obtained from the patient for publication of this article.

## Conflict of Interest

Authors declare no conflict of interest.

## Data Availability

All relevant data are within the paper and its Supporting Information files.