

Intravascular Large Cell non-Hodgkin Lymphoma in Subacute-Chronic Subdural Hematoma: a case report

Linfoma não Hodgkin Intravascular de Grandes Células em Hematoma Subdural Subagudo Crônico: relato de caso

Linfoma no Hodgkin de Células Grandes Intravascular en Hematoma Subdural Subagudo-Crónico: reporte de un caso

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Abstract

Introduction: Intravascular lymphoma (IVL) is a rare subtype of non-Hodgkin extranodal lymphoma with characterized by a positive CD20 B cell proliferation in small lumens and medium-sized blood vessels, except veins and large arteries. Blood vessels in the central nervous system (CNS) and the skin is most often affected. These tumors usually occur in older adults and aggressive. **Methodology:** Descriptive study of the case report type, whose data were obtained from the patient's medical record and has received the patient's consent to be published. **Case presentation:** This paper reports a 63-year-old man, who suffered Parkinson disease and neurological symptoms for 6 months. From imaging, there is a chronic subacute subdural hematoma in the right frontotemporoparietal area. Operation performed, histopathological examination of the tissue with Hematoxylin-Eosin staining and immunohistochemical examination confirmed diagnosis Intravascular Large Cell non-Hodgkin Lymphoma (IVLCL) type B-cell CD20 (+) in subacute-chronic subdural hematoma (SDH). **Discussion:** This tumor is characterized by selective growth of lymphoma cells within the lumen of blood vessels, particularly capillaries, and with the exception of the larger arteries and veins, occurred in adults, with a median age of 67 years. Sixty five percent show neurological symptoms with rapidly progressive cognitive dysfunction or subacute dementia. The cause of chronic SDH in this patient is unknown, but it can occur due to increasing age, brain atrophy, and enlargement of the subdural space, relatively minor trauma. **Conclusion:** This lymphoma is aggressive with a poor prognosis but a chemotherapy regimen with rituximab significantly improves the clinical outcome of this patient, with an overall survival of 3 years 60-81%.

Keyword: Lymphoma; Intravascular; Subdural hematoma.

Resumo

Introdução: O linfoma intravascular (LIV) é um subtipo raro de linfoma extranodal não Hodgkin, caracterizado por proliferação positiva de células B CD20 em pequenos lúmens e vasos sanguíneos de médio porte, exceto veias e grandes artérias. Os vasos sanguíneos no sistema nervoso central (SNC) e a pele são mais frequentemente afetados. Esses tumores geralmente ocorrem em adultos mais velhos e agressivos. **Metodologia:** Estudo descritivo do tipo relato de caso, cujos dados foram obtidos do prontuário do paciente e recebeu o consentimento do paciente para publicação. **Apresentação do caso:** Este trabalho relata um homem de 63 anos, que sofria de doença de Parkinson e sintomas neurológicos há 6 meses. Na imagem, há um hematoma subdural subagudo crônico na área frontotemporoparietal direita. Operação realizada, exame histopatológico do tecido com coloração de Hematoxilina-Eosina e exame imunohistoquímico confirmaram o diagnóstico Linfoma não Hodgkin Intravascular de Grandes Células (IVLCL) tipo B de

células B CD20 (+) em hematoma subdural subagudo crônico (SDH). Discussão: Este tumor caracteriza-se pelo crescimento seletivo de células do linfoma no interior da luz dos vasos sanguíneos, principalmente capilares, e com exceção das artérias e veias maiores, ocorrendo em adultos, com idade média de 67 anos. Sessenta e cinco por cento apresentam sintomas neurológicos com disfunção cognitiva rapidamente progressiva ou demência subaguda. A causa da HSD crônica neste paciente é desconhecida, mas pode ocorrer devido ao aumento da idade, atrofia cerebral e aumento do espaço subdural, trauma relativamente menor. Conclusão: Este linfoma é agressivo e de mau prognóstico, mas um regime quimioterápico com rituximab melhora significativamente a evolução clínica deste paciente, com sobrevida global de 3 anos 60-81%.

Palavras-chave: Linfoma; Intravascular; Hematoma subdural.

Resumen

Introducción: El linfoma intravascular (LIV) es un subtipo raro de linfoma extraganglionar no Hodgkin que se caracteriza por una proliferación de células B CD20 positivas en luces pequeñas y vasos sanguíneos de tamaño mediano, excepto venas y arterias grandes. Los vasos sanguíneos del sistema nervioso central (SNC) y la piel son los más afectados. Estos tumores suelen presentarse en adultos mayores y de forma agresiva. Metodología: Estudio descriptivo del tipo reporte de caso, cuyos datos fueron obtenidos de la historia clínica del paciente y ha recibido el consentimiento del paciente para ser publicados. Presentación de caso: Este artículo reporta un hombre de 63 años, quien padeció enfermedad de Parkinson y síntomas neurológicos durante 6 meses. De las imágenes, hay un hematoma subdural subagudo crónico en el área frontotemporoparietal derecha. Operación realizada, examen histopatológico del tejido con tinción de hematoxilina-eosina y examen inmunohistoquímico confirmaron el diagnóstico de linfoma no Hodgkin intravascular de células grandes (IVLCL) tipo B de células CD20 (+) en hematoma subdural crónico subagudo (SDH). Discusión: Este tumor se caracteriza por el crecimiento selectivo de células de linfoma dentro de la luz de los vasos sanguíneos, en particular los capilares, y con la excepción de las arterias y venas más grandes, se presentó en adultos, con una mediana de edad de 67 años. Sesenta y cinco por ciento muestran síntomas neurológicos con disfunção cognitiva rápidamente progresiva o demencia subaguda. Se desconoce la causa de la SDH crónica en este paciente, pero puede ocurrir debido al aumento de la edad, atrofia cerebral y agrandamiento del espacio subdural, trauma relativamente menor. Conclusión: Este linfoma es agresivo y de mal pronóstico, pero un régimen de quimioterapia con rituximab mejora significativamente el resultado clínico de este paciente, con una supervivencia global de 3 años 60-81%.

Palabra clave: Linfoma; Intravascular; Hematoma subdural.

1. Introduction

Intravascular lymphoma (IVL) is a rare subtype of extranodal non-Hodgkin lymphoma. In 1959 it was known as systemic angioendotheliomatosis of the skin vessels. This tumor was later reclassified as IVL and subsequently recognized as a distinct entity in the World Health Organization (WHO) tumor classification. IVL has an estimated annual incidence of 0.5 cases per 1,000,000 population. IVL is characterized by proliferation of CD20 positive B cells in the lumen of small and medium-sized blood vessels, except for large veins and arteries. Blood vessels in the central nervous system (CNS) and skin are most commonly affected. Large B-cell intravascular lymphoma is a large extranodal B-cell lymphoma that usually occurs in older adults and usually follows an aggressive clinical course, with many patients diagnosed at perimortem or postmortem examination. Approximately one third of patients present with neurologic symptoms. Patients with CNS involvement may present with rapidly progressive cognitive dysfunction or subacute dementia. Other nonspecific symptoms include fever, anemia, and thrombocytopenia. Radiographically, no mass lesion was seen. Cerebral or cerebellar hemorrhage from IVL is very rare. IVL cases with intracerebral hemorrhage with a cause of bleeding were never identified, even from histopathological examination. It is suspected that chronic degenerative or inflammatory changes of the vessel wall, such as hyalinization, fibrosis, and fibrinoid necrosis, cause bleeding. The following reports a case of a 63-year-old man with Parkinson's disease and neurological deficits, with imaging results showing a subacute chronic subdural hematoma in the right frontotemporoparietal area. This case is unique in that an incidental intravascular lymphoma was found on a brain biopsy with a chronic subacute subdural hematoma.

2. Methodology

Descriptive study of the case report type, whose data were obtained from the patient's medical record and has received the patient's consent to be published.

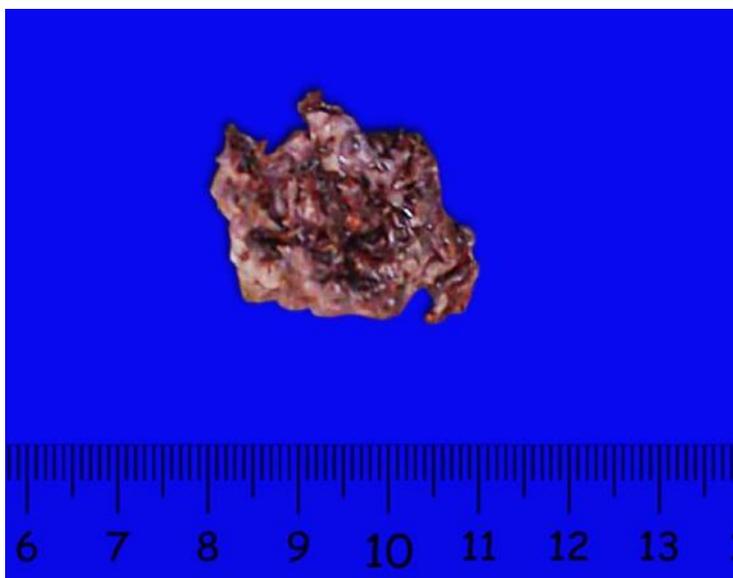
3. Case Presentation

A 63-year-old male patient came to the hospital with the chief complaint of left limb weakness, shaking hands, difficulty speaking for the last 6 months. Symptoms are said to be getting worse since the last 2 weeks, accompanied by headaches that do not improve with rest. On physical examination, GCS (E3V4M5) was found, respiration 16 times/minute, pulse 70x/minute, temperature 36.6 °C, blood pressure 150/100 mmHg. Neurological examination revealed the impression of left nerve VII paresis, left flaccid hemiparesis impression, left Babinski reflex.

The patient underwent head MRI and cerebral angiography. MRI of the head showed a chronic subacute subdural hematoma in the right frontotemporoparietal area, with a maximum thickness of 2.7 cm, compressing the right lateral ventricle and a midline shift to the left of 7.98 mm. Cerebral angiography showed no abnormalities.

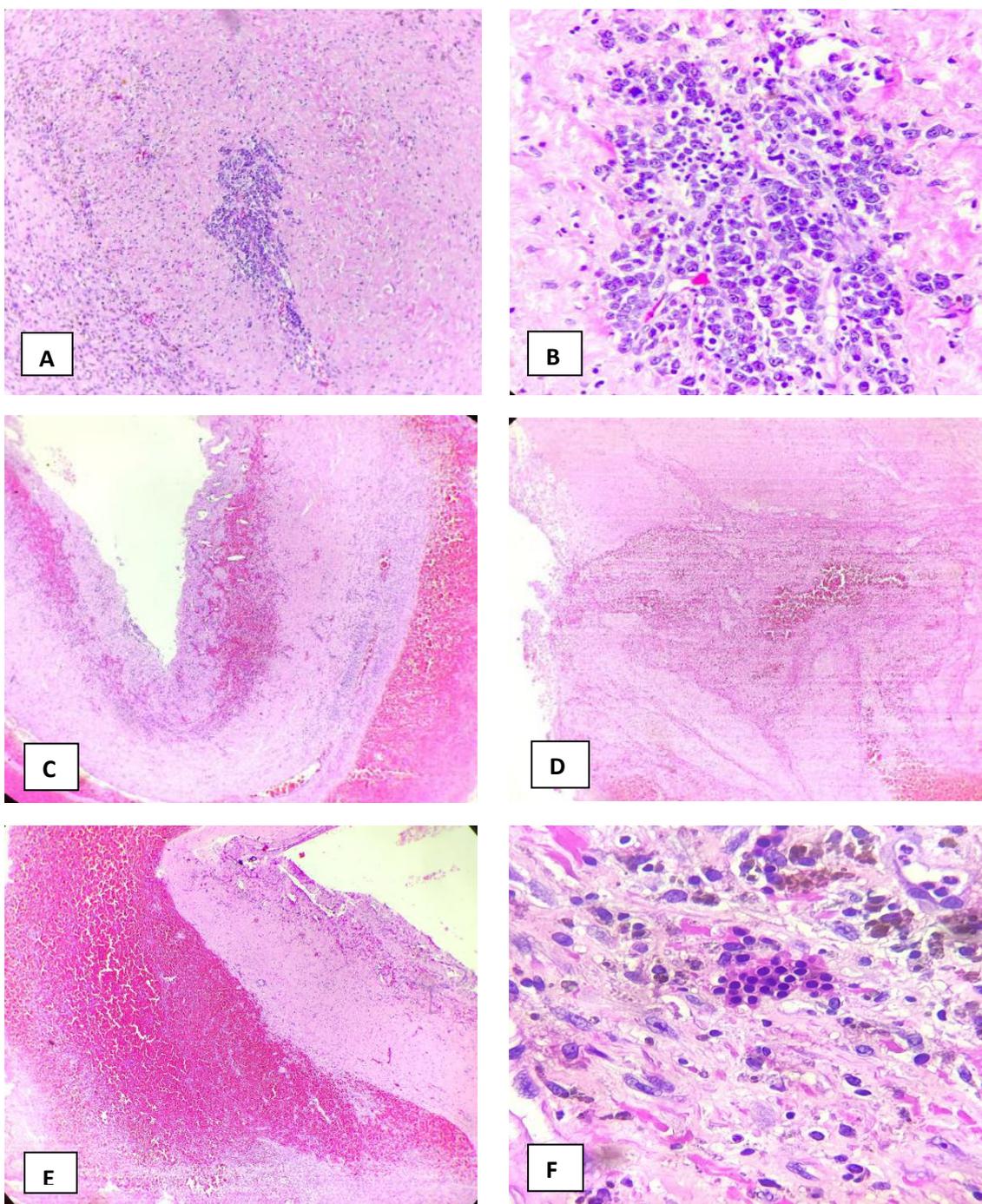
With the results of the MRI examination, the patient was indicated for surgery. The surgical tissue was taken to the anatomical pathology laboratory for routine histopathological examination. On macroscopic examination, received 1 piece of tissue in the form of a cyst that has been split in a 10% NBF solution (neutral buffered formalin 10%), accompanied by a patient identification label, the tissue with a size of 3 x 3 x 1 cm. On the slices appear gray white tissue and some reddish.

Figure 1. Tissue macroscopic.



Source: Authors.

Figure 2. Tissue microscopy. A. Clusters of medium to large spherical cells (lymphoid cells) around and intracapillaries (HE, 100x) B. These cells have round nuclei oval to ovoid, cleave and noncleaved, vesicular chromatin with multiple prominent nuclear near the nuclear membrane (centroblast cell) (HE, 400x). C, D, E. Inflamed granulation tissue containing many components of blood vessels, extravasation of erythrocytes and myofibroblast cells (HE, 100x). F. Thin collagen bundles form a fascicle structure, parallel oriented, containing fibroblast cells, blood vessels, hemosiderin pigment and scattered lymphoplasmic and eosinophil inflammatory infiltrate, suggesting fibrotic tissue (HE, 400x).



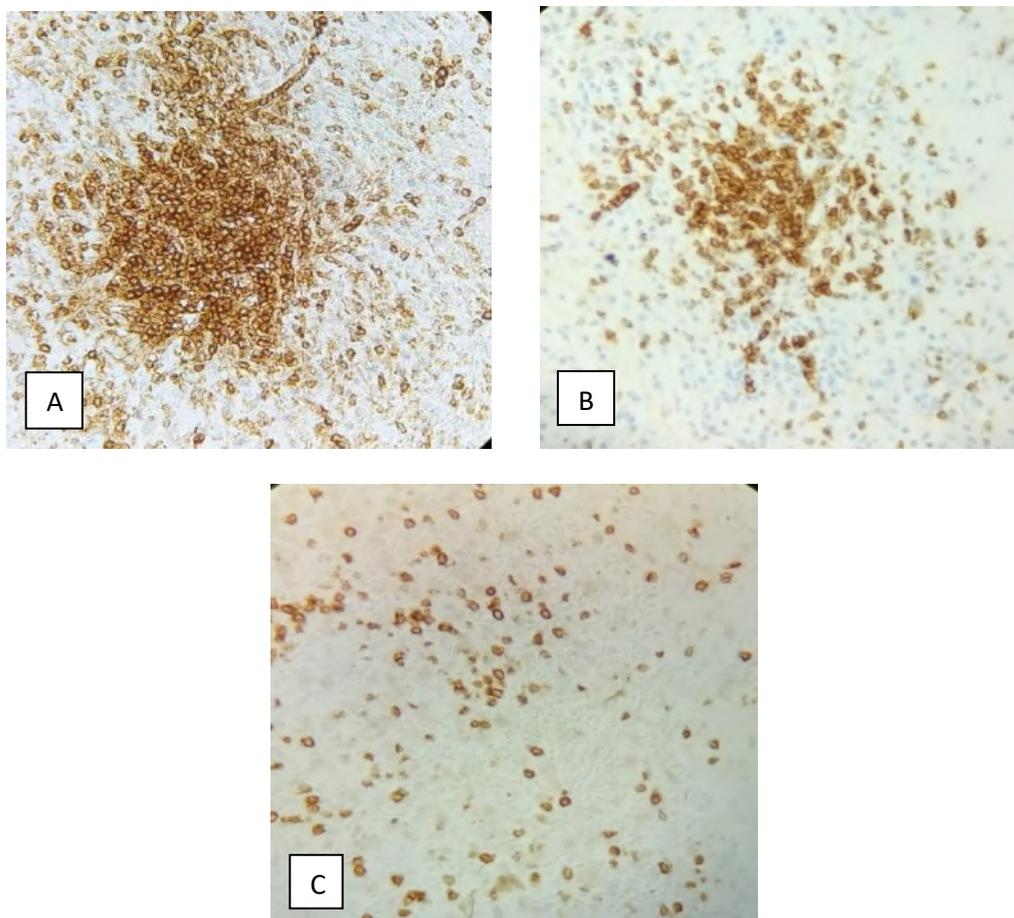
Source: Authors.

On microscopic examination with HE staining, it was found that some of the tissue showed thin collagen bundles forming a fasciculus structure, oriented parallel, containing cells suitable for the image of fibroblast cells, blood vessels arranged perpendicularly, hemosiderin pigment and scattered lymphoplasmic and eosinophil inflammatory infiltrates, suggesting fibrotic tissue. Others are in the form of inflamed granulation tissue which contains many components of blood vessels, extravasation of erythrocytes and myofibroblast cells. There is also an extensive hematoma consisting of organized erythrocytes and fibrin. At one particular microscopic focus, clusters of medium to large spherical cells (lymphoid cells) appear around the capillaries and intracapillaries, these cells have oval to ovoid spherical nuclei, cleaved and noncleaved, vesicular chromatin, multiple prominent nuclei near the nuclear membrane (centroblast cell). The morphological appearance suggests a subacute-chronic subdural hematoma with a microscopic focus of atypical large lymphoid like cells intracapillary, the diagnosis tends to be Intravascular large cell non-Hodgkin Lymphoma (IVLCL) in subacute-chronic subdural hematoma (SDH).

Determination of the diagnosis was carried out by immunohistochemical (IHC) examination of CD45, CD20, CD3. CD45 was stained on mature lymphocytes and tumor cells, CD20 was stained with tumor cells, and CD3 was non-specific on mature lymphocytes. Based on the immunohistochemical staining pattern, it showed Non-Hodgkin Lymphoma type B cells with positive CD20.

Through the correlation of clinical examination, imaging findings, histopathological and immunohistochemical features, this case was diagnosed as Intravascular large cell non-Hodgkin Lymphoma (IVLCL) type B cells positive CD20 in subacute-chronic subdural hematoma (SDH).

Figure 3. Immunohistochemistry. A. CD45 stain, stained on mature lymphocytes and tumor cells (400x). B. CD20 stain, stained on tumor cells (400x). C. CD3 staining, non-specific staining on mature lymphocytes (400x).



Source: Authors.

4. Discussion

Intravascular large B cell lymphoma is a rare type of extranodal large B cell lymphoma characterized by selective growth of lymphoma cells within the lumen of blood vessels, particularly capillaries, and with the exception of the larger arteries and veins (Deckert et al., 2021; Nakamura et al., 2017). This highly aggressive type of lymphoma, once incorrectly referred to as "neoplastic angioendotheliomatosis," is an extranodal DLBCL (very rarely T-cell lymphoma) characterized by lymphoma cells that are entirely or almost entirely within the lumina of small blood vessels, especially capillaries (Perry & Brat, 2018). IVL has an estimated annual incidence of 0.5 cases per 1,000,000 population (Fonkem et al., 2016). The etiology of this disease is unknown, a possible explanation for chemokines receptor interactions, for example CXCL9 (expressed in the endothelium) and CXCR3 (expressed in IVLBCL), decreased expression of adhesion molecules on the cell surface of IVLBCL, CD29 and CD54 (Miranda, 2018).

These tumors occur in adults, with a median age of 67 years (range: 13-85 years) and a male-to-female ratio of 1.1:1 (Nakamura et al., 2017). IVL usually occurs in older adults and usually follows an aggressive clinical course, with many patients diagnosed at perimortem or at postmortem examination. This case occurred in a 63-year-old male patient.

IVL can involve any organ system, with blood vessels in the central nervous system (CNS) and skin most commonly affected. These cells have lost the ability for transvascular migration due to defects in the adhesion molecules. IVL in the

central nervous system has various neurological manifestations that often hinder the diagnosis (Chen et al., 2020). Approximately 30% of patients present with CNS symptoms, and 65% present with neurological symptoms as the main manifestation of the disease course. Patients with CNS involvement may present with rapidly progressive cognitive dysfunction or subacute dementia. Other nonspecific symptoms include anemia, fever and thrombocytopenia (Lauw et al., 2020). Occlusion of blood vessels by tumor cells causes infarction (Perry.& Brat, 2018). Patients may develop subacute encephalopathy or dementia, paralysis, seizures, or multifocal cerebrovascular events. Systemic symptoms vary, but fever and skin lesions are the most common, whereas lymphadenopathy is usually absent (Chen et al., 2020). The clinical signs of IVL are generally non-specific and can progress very rapidly. Thus, the prognosis of IVL remains uncertain. Approximately 60% of IVL cases in the CNS, are diagnosed at post mortem examination (Uzuka et al., 2018).

Radiographically, no mass lesion is visible, but FLAIR or T2 abnormalities may occur. IVL imaging studies in the brain are characterized by multiple hyperintense white matter lesions on T2-weighted images, resembling ischemic or demyelinating lesions. Cerebral or cerebellar hemorrhage due to IVL is very rare (Uzuka et al., 2018). Although various patterns of abnormal brain MRI features in patients with IVLBCL have been reported, a recent study suggested findings on brain MRI and categorized them into 4 patterns, namely: (1) non-specific white matter lesions, (2) infarct-like lesions, (3) hyperintense lesions in the pons, and (4) meningeal thickening and/or enhancement (Wu et al., 2021; Matsue et al., 2019).

In this case, the patient had neurological symptoms since the last 6 months and the symptoms had gotten worse since the last 2 weeks. While on MRI examination there was no mass, only a chronic subacute subdural hematoma (SDH) was found. SDH is an encapsulation of both liquid blood pools and blood degradation products between the dura and the arachnoid layer of the brain resulting from injury to the venous bridge that traverses the subdural space (Edlmann et al., 2017). The most frequent risk factor is head injury (Shapey et al., 2016). Other risk factors include the use of antiplatelet or anticoagulant drugs, coagulopathy, hematologic malformations or vascular malformations. The incidence of SDH cases increases sharply in the 6th and 7th decades of life (Cheng et al., 2014). With increasing age, brain atrophy, and enlargement of the subdural space, minor trauma can cause subdural hemorrhage (Shapey et al., 2016). The clinical picture differs in the patient's age group, can be asymptomatic, impaired cognitive function, severe neurological deficits, or even life-threatening herniation (Cheng et al., 2014). Subdural hematomas can be categorized into acute, subacute, and chronic. Subdural hematoma is said to be acute if it appears within 3 days after bleeding, subacute subdural hematoma appears within four to twenty days after bleeding, and chronic subdural hematoma appears anytime after twenty days of bleeding (Alshora et al., 2018). Asymptomatic and mild cases of SDH can usually be treated medically. However, in moderate to severe cases, or when the clinical course is deteriorating, surgical intervention is required. Recurrent subdural hematomas may also be an indication for surgical intervention when there is re-accumulation of bleeding causing symptoms. In addition, a subdural hematoma larger than 10 mm, a change in mental status and dilatation of both pupils, or an extensor posture requires immediate surgical intervention (Alshora et al., 2018). The recurrence rate of chronic SDH is said to be quite high, in recent decades reaching 33.3%, but many studies show a recurrence rate of 10-15% (Uno et al., 2017).

IVL itself was previously categorized into 2 types according to geography, namely Western and Asian (Ong et al., 2021). However, based on the clinical picture, it is divided into 3 variants, namely the classic variant, the cutaneous variant, and the variant associated with hemophagocytic syndrome. The classic variant is characterized by symptoms corresponding to the organ involved. The cutaneous variant is limited to skin lesions without other systemic involvement and is associated with a better prognosis. The hemophagocytic syndrome-associated variant has the worst prognosis because it is associated with hemophagocytosis and multiorgan failure (Ong et al., 2021). This case involves the brain so it can be a classic variant of IVL.

Microscopically, IVL is neoplastic lymphoid cells located mainly in the lumen of small to medium-sized blood vessels in many organs. In some cases, fibrin thrombi, hemorrhage, and necrosis may be seen. Tumor cells are large, with

conspicuous daughter nuclei and many mitoses. Minimal extravascular neoplastic cell locations may be seen. In the CNS, recurrence is associated with extravascular brain mass (Nakamura et al., 2017). In this case, microscopically found a single focus group of medium to large spherical cells (lymphoid cells) around the capillaries and intracapillaries, these cells have oval to ovoid spherical nuclei, cleaved and noncleaved, vesicular chromatin. with multiple prominent nuclei near the nuclear membrane (centroblast cell).

Tumor cells express mature B cell-associated antigens, namely CD19, CD20, CD22, CD79- α , and pax-5 (Nakamura et al., 2017; Miranda, 2018). In addition, tumor cells also expressed CD5 and CD10, coexpression was seen in 38% and 13% of cases, respectively. Bcl-6 positive 25%, Bcl-2 positive 90%, MUM1/IRF-4 positive. Ki-67 was high, indicating high proliferative activity. CD2 negative, CD3 negative (Miranda., 2018). In this case, immunohistochemistry (CPI) examination of CD45, CD20, CD3 was performed. CD45 was stained on mature lymphocytes and tumor cells, CD20 was stained with tumor cells, and CD3 was non-specific on mature lymphocytes. Based on histopathological and immunohistochemical examination, it was suitable for Intravascular large cell non-Hodgkin Lymphoma (IVLCL) type B cells CD20(+) in subacute-chronic subdural hematoma (SDH).

The differential diagnosis for IVL cases in general is hepatosplenic T-cell lymphoma, large T-cell granular lymphocytic leukemia, aggressive NK cell lymphoma/leukemia, marginal zone splenic B-cell lymphoma (Miranda, 2018). The few reported cases of intravascular T-cell lymphoma are -T-cell lymphoma or hepatosplenic T-cell lymphoma, more frequently in young men, with splenomegaly and hepatomegaly. Bone marrow biopsy revealed small to medium-sized lymphoma cells, intranuclear pattern (in the early stages of the disease), large cell blastic lymphoma with an interstitial or diffuse pattern (in late stages). The T cell markers were CD2 and CD3 positive and the cytotoxic marker TIA positive, GZM-B positive, B-cell marker negative. Large T cell granular lymphocytic leukemia is usually associated with infection, peripheral blood may show an increase in large granular lymphocytes, bone marrow usually in an interstitial pattern, partially sinusoidal, CD8 positive, GZM-B positive, perforin positive, CD16 positive, CD57 positive, CD5 positive. Leukemic cells may have cytoplasmic azurophilic granules, positive NK cell marker, positive GZM-B, positive perforin, EBV positive or negative, surface CD3 negative, CD5 negative. T cell lymphoma or NK cell lymphoma can be intravascular, usually positive for T or NK cell markers, this rare lymphoma does not exist as a diagnostic category in the WHO classification. Marginal zone splenic B cell lymphoma with white and red pulp infiltrate, small neoplastic cells with abundant pale cytoplasm, patient often presents with cytopenia, lymphocyte villi appear on peripheral blood smear, marker pan-B-cell positive, CD3 negative, CD10 negative (Miranda, 2018).

Intravascular large B-cell lymphoma is generally aggressive, except for cases with limited disease to the skin (Nakamura et al., 2017). The poor prognosis is partly due to the delay and accuracy of diagnosis associated with the various presentations of these lymphomas. In addition, several risk factors were identified as giving a poor prognosis, including lactic dehydrogenase (LDH) levels $>700\text{U/L}$, CNS involvement, and hemophagocytic syndrome (HPS) (Liu et al., 2020). The clinical picture of IVLBCL is heterogeneous among patients which causes difficulties in early diagnosis. Early diagnosis and treatment can increase the success of therapy in IVLBCL cases. Although there is currently no consensus on a diagnostic protocol, randomized skin biopsy remains the most frequently performed strategy for patients with suspected IVLBCL (Ong et al., 2021). The most effective IVL treatment in the CNS at present is a combination of methotrexate (MTX)-based intrathecal chemotherapy and R-CHOP. Lower doses of the drug may be used because they penetrate the blood-brain barrier, and produce minimal systemic toxicity. Intrathecal chemotherapy should also be used as prophylaxis in patients without CNS involvement (Nizamutdinov et al., 2017). Chemotherapy regimens with rituximab were said to significantly improve clinical outcomes in these patients, with an overall 3-year survival of 60-81% (Nakamura et al., 2017; Miranda, 2018).

5. Conclusion

Intravascular lymphoma (IVL) is a rare subtype of extranodal non-Hodgkin's lymphoma. Intravascular large B cell lymphoma is generally aggressive. The poor prognosis is due in part to the delay and accuracy of diagnosis associated with the diverse presentation of these lymphomas, and the heterogeneous clinical picture that makes early diagnosis difficult. In this case, IVL was found incidentally in the case and the symptoms were associated with a chronic subacute subdural hematoma. With the immediate discovery of the presence of intravascular lymphoma in this patient, it is hoped that it can increase survival expectations with an adequate therapeutic regimen.

It is hoped that in the future there will be more studies of early detection of IVL and advanced therapy in order to increase the survival rate of patients with these cases.

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