A case report of B lymphoblastic lymphoma with brain metastases
Clinical and pathological significance of head trauma misdiagnosis

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Abstract
Introduction: B lymphoblastic lymphoma (B-LBL) is a rare type of lymphoma that originates from precursor lymphocytes. B-BLB in adults with brain metastases is extremely rare as the disease mainly affects children and adults. Therefore, such a seldom-seen case can easily trigger a dispute regarding clinical diagnosis and treatment.

This paper reports the case of a 22-year-old man hospitalized for a head injury that resulted from a physical altercation. Upon admission to the hospital, the patient was diagnosed with a diffuse axonal injury (DAI). Accordingly, the patient receiving follow-up treatments, but died 30 days later. After a systematic necropsy, immunohistochemical staining, radiological consultation, and a complete review of the clinical dates, we defined the case as a brain metastasis of B lymphoblastic lymphoma. Imaging results of the intracranial lymphoma were nearly indistinguishable from DAI during the acute phase, which led to misdiagnosis and incorrect treatment for B-LBL.

Conclusion: We present this case to broaden the scope of pathologic and clinical diagnosis for intracranial tumors and to inform physicians, general neurologists, and even medical examiners with an added degree of differential awareness in dealing with the clinical materials before further diacrisis and disposal.

Abbreviations: $\beta$-APP = $\beta$-site amyloid precursor protein, BL = Burkitt lymphoma, B-LBL = B lymphoblastic lymphoma, CBC = complete blood count, CNS = central nervous system, CT = computer tomography, DAI = diffuse axonal injury, LBL = lymphoblastic lymphoma, MPO = myeloperoxidase, MRI = magnetic resonance imaging, TdT = terminal deoxynucleotidyl transferase, T-LBL = T lymphoblastic lymphoma, WBC = white blood cell.

Keywords: B lymphoblastic lymphoma, clinical pathology, craniocerebral injury, immunohistochemical examination, pathological diagnosis

1. Introduction
Lymphoblastic lymphoma (LBL), an unusual neoplasm of high malignancy and generally features rapid progression, high mortality, and is most common in children and teenagers under the age of 20.\textsuperscript{[1]} Based on cell lineage, World Health Organization (WHO) divides LBLs into 2 broad categories as T lymphoblastic lymphoma (T-LBL) and B lymphoblastic lymphoma (B-LBL).\textsuperscript{[2]} Approximately 90% of precursor lymphoid neoplasms assume a T-cell phenotype and occur mainly in male adolescents. The primary clinical manifestations include mediastinal masses, lymph node enlargement, and bone marrow and central nervous system involvement. The B-cell phenotype, which is much less prevalent than T-LBL, is also commonly found in children.\textsuperscript{[3]} Extramedullary involvement is common, with a preference for the central nervous system, lymph nodes, soft tissue, and spleen,\textsuperscript{[4]} but metastases only present in the brain.

We now depict a case of a young man misdiagnosed with DAI following head trauma. Thirty days post-admission, the patient died and necropsy revealed multiple brain metastasis of B-LBL which caused central nervous system (CNS) failure and death.

1.1. Case presentation
A 22-year-old man was admitted to the hospital with complaints of headache and dizziness coupled with a transient unconsciousness after an external head trauma 2 days prior. Physical examination presented as normal except for a slightly reduced mental state. Laboratory investigation showed a normal white
blood cell (WBC) count of $5.63 \times 10^9/L$ and lymphocyte rate of 20.00%. An intraday magnetic resonance imaging (MRI) revealed multipatchy long T1 and T2 signals in the basal ganglia, bilateral frontal lobes, brain stem, and genu of corpus callosum (Fig. 1A). Despite 10-day symptomatic treatment in accordance with the first-time diagnosis of DAI, the patient’s condition continuously worsened. Twelve days post-injury, MRI showed multiple abnormal signals in the medulla oblongata, midbrain, bilateral cerebral ganglion, right frontal lobe, and corpus callosum (Fig. 1B). Sixteen days post-injury, the man gradually developed conscious disturbance and dyskinesia combined with myodynamia loss of his lower limbs. He was then transferred to a more specialized hospital and upon physical examination, the patient was confused, lethargic, and slurring his speech. Myodynamia check demonstrated grade IV of the higher limbs and grade III of the lower limbs. Admitting diagnosis was still affirmed as DAI. Twenty-one days post-injury, complete blood count (CBC) showed the WBC count of $7.00 \times 10^9/L$ and lymphocyte rate of 14.60%. Therapeutic prescription remained the same as before. However, the patient’s condition continued to deteriorate. In the next few days, MRI identified multiple abnormal brain signals with a pronounced enhancement (Fig. 1C). The absolute value of WBCs considerably rose to $35.0 \times 10^9/L$ and lymphocyte rate of 49.40%. One week later, the patient was pronounced dead after attempted rescue. Prior written and informed consent were obtained from the patient’s family and the study was approved by the ethics review board of The Tongji Hospital.

1.2. Autopsy and histopathological examination

The skull was intact with no observed subdural hematoma or subarachnoid hemorrhage. The brain was swollen and weighed 1400 g. The transtentorial and tonsillar herniation was formed. Microscopically, the arachnoid membrane showed a focal thickness, and a significant amount of tumor cells were perivascular and exclusively infiltrated the subarachnoid space, molecular cortical, and external granular layers. Small pieces of hemosiderin were sporadically deposited in the cerebellum subarachnoid space. Tumor cells were diffusely distributed in the optic chiasma, optic nerve, mammillary body, capsula interna, basal ganglion, and brain stem, and the boundaries were blurred. Hypertrophy and proliferation of astrocytes were detected. Tumor invasion of the corpus callosum, cingulate gyrus, superior frontal gyrus, central gyrus, and parahippocampal gyrus took the form of a perivascular cuff around the blood vessels and were scattered in the peripheral parenchymal. There were different quantities of tumor cells in the nerve roots of the medulla oblongata and cervical cord. At high power, the morphology of tumor cells was small to medium sized with randomly shaped cell nuclei, point-shaped chromosomes, and irregular mitosis.

In other organs, tumor cells that infiltrated vessels gathered in the capillaries and interstitium of the faecal tonsil, and neutrophils had been infiltrated in the crypt palatine tonsil. Tumor embolus could be seen in the capillaries of the alveolar walls and pulmonary small vessels. Diffuse invasion was also evident in the splenic cord and renal interstitium. Limited invasion was inspected in the sinus hepaticus, stroma glandulae thyreoideae, and colonic mucosa.

1.3. Immunohistochemical study

Immunohistochemical staining of the tumor cells was positive for terminal deoxynucleotidyl transferase (TdT), CD20, CD43, and CD99 but negative for myeloperoxidase (MPO), CD3, and CD7. As for the optical nerve, corpus callosum, and brain stem, β-site amyloid precursor protein (β-APP) reflected a negative finding (Fig. 2).

1.4. Pathologic diagnosis and death causes

Based on the morphological findings and immunohistochemical examination, the final diagnosis was B-LBL with systemic metastasis. The cause of death was due to systemic metastasis of CNS resulting in functional failure, predominately due to extensive brain metastasis of this lesion.

2. Discussion

In an American study, the incidence of LBL was 0.1–0.2/100,000 per year while B-LBL comprises approximately 10% of all LBLs.[5] Being a type of high-grade malignant lymphoid neoplasm that originates from precursor B cells, B-LBL has clinical manifestations such as diffuse hyperplasia of the tumorous lymphoblast in the bloodstream. It replaces the existing myeloid tissue and infiltrates systemically, most notably lymph nodes, liver, and spleen. In this case, multiple organ
metastases affected brain, palatine tonsil, thyroid, lung, spleen, liver, kidney, and colonic mucosa. On a separate note, the growth pattern of neoplastic cells in its various metastatic foci revealed various features: B lymphoblast cells of the mammillary body, capsula interna, globus pallidus, hippocampus, pons, optic nerve, and cervical cord were widely scattered yet clumped together as patchy lesions in other regions. This variation of cell growth may be due to a variety of factors such as differentiation and development of tumor cells, immunogenicity, blood flow velocity, and fibrous content of target organs.

CNS invasiveness, particularly intracranial invasion of B-LBL is closely related to bone marrow metastases, the poor prognosis of which is associated with the proportion of tumor cells present in bone marrow.[6] Typically, B-LBL originates in the lymph nodes in the form of enlargement during onset while the peripheral hemogram and myelogram remain normal, but advanced brain metastases are more common. The general condition of this patient revealed as tolerable after injury. Despite the abnormal results of cranial imaging, CBC did not indicate a probable risk of intracranial tumors until the anabatic WBCs, and increased ratio of lymphocyte was mentioned in the later review. Here we broadly detected the encephalic attack under the microscope.

Imaging differential diagnosis between injury and illness addresses the central issue of this case in clinical practice. It is imperative to comprehensively master the medical history and succession imaging via MRI or computer tomography (CT) examination for trauma diagnosis or differential diagnosis from the other intracranial lesions after cranio-cerebral injury.[7] The results progressively presented the apparent inconformity with prospect ion, which could be a reason for the possibility of misdiagnosis. If prospect ion is considered alongside the clinical symptoms and completed accessory examinations, such as bone marrow smear and lumbar puncture, then diagnostic accuracy could be better achieved.[8] MRI and CT scanning have limitations compared with histopathological examination of brain metastases of B lymphoblastic lymphoma, diffuse axonal injury, and other central nervous system neoplasms.[9,10] Therefore, diagnosis and treatment for this category of patients should not be entirely dependent upon imaging, although general neuroimaging is still very important in the identification of DAI and other similar diseases. Correlation can be found between the radiological appearances and histological classification for different disease categories. These correlations will provide valuable clues to more definitive diagnosis and treatments.[11] As for the differential determination of diseases such as DAI, lymphoma, and blood diseases, immunohistochemical examination with suitable antibodies is a standard procedure for diagnosis.[12] Deterministic diagnosis of B-LBL is mainly dependent on immunohistochemistry[13] about 95% of lymphoma cells express TdT as a primitive lymphocyte marker and some B cell differentiation antigens. Moreover, it is a requisite for B-LBL to differentiate from T-LBL and Burkitt lymphoma (BL).[14] Definite
classification in histopathology is not feasible; however, immunophenotyping pointed at a B cell phenotype as CD20, CD43, and CD99 reflect a positive result. Furthermore, the positive result of TdT denotes B-LBL instead of BL. Immunohistochemical studies tend to indicate DAI, but since axonal retraction ball and β-APP tested negative, we excluded the possibility of DAI.

3. Conclusions
Throughout this case, the following items should be weighted when clinicians encounter cranio-cerebral injuries, especially when there is a potential diagnosis of DAI or other intracranial neoplastic diseases. Firstly, before the final diagnosis and treatment, a full grasp of the patient’s medical record is required before a cohesive treatment plan is chosen. The records should contain the patient’s prior medical examination, family history, and any additional relevant information for a comprehensive understanding of the patient’s physical condition. To avoid a misdiagnosis, all physicians who encounter this category of patients should have some familiarity with clinical features and imaging characteristics of CNS lymphoma, the correct interpretation of which could also avoid an excessive number of unnecessary brain MRIs. Spinal cord and lymph node extraction, and bone marrow smear are important to clarify the conjecture. A comprehensive analysis containing the competition between trauma and illness after the above inspections may require consultation with clinical and auxiliary departments.

Neuropathy occurs with various manifestations as a consequence of trauma, lymphoma, and other neoplasms. An understanding of the etiology is still necessary for diagnosis and proper treatment. Eventually, this case reminds us that clinical judgment and experience can provide a useful initial basis for classification, in so far as it represents what clinicians perceive to be a valuable way of categorizing patients. However, the value of such classifications cannot be assumed without empirical evidence of utility that only pathological diagnosis can provide. Then it supplies the gold standard against which other case definitions can be assessed.

Author contributions
YWZ performed the pathology and histological examination. JS contributed to the medical records findings and gave information about clinical history. SW, JM, and PV helped to the final draft of the manuscript. All authors read and approved the final manuscript.

Funding acquisition: Song Wu.
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Supervision: Yiwu Zhou, Song Wu.
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Writing – review & editing: Jale Manzo, Agovino Peter.

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