De novo primary malignant lymphoma of the dura following recurrent episodes of subdural abscess presenting as chronic subdural hematoma: illustrative case

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BACKGROUND Chronic inflammation of the thorax, as in tuberculosis-related pyothorax, can cause secondary malignant lymphomas. However, primary malignant lymphoma of the central nervous system, specifically of the dura mater, developing after intracranial infection or inflammation has rarely been reported. Herein, the authors describe a case of primary dural lymphoma that developed secondary to subdural empyema, with an initial presentation mimicking a chronic subdural hematoma.

OBSERVATIONS A 51-year-old man had undergone single burr hole drainage for subdural empyema 2 years prior. The patient subsequently underwent multiple craniotomy and drainage procedures, with successful remission of the subdural empyema. He was subsequently referred to the authors’ hospital approximately a year after his initial treatment because of a recollection of subdural fluid, which was suspected to be recurrent empyema. After another single burr hole drainage, which revealed only a subdural hematoma, a histopathological diagnosis of B-cell lymphoma of the dural/subdural membrane was made. Subsequent radiation therapy was completed, with good local control and no recurrence of the subdural hematoma confirmed at 2 months posttreatment.

LESSONS Intracranial lymphoma triggered by chronic inflammation is rare but should be considered a differential diagnosis in subdural hematomas for which the background pathology is unclear.

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KEYWORDS secondary dural lymphoma; primary central nervous system lymphoma; subdural empyema; B-cell lymphoma; case report

Malignant lymphomas originating from the thorax secondary to chronic inflammation, such as that caused by pyothorax, have been frequently reported.1 However, reports of primary central nervous system lymphoma (PCNSL) associated with intracranial infection or hematoma are rare. Herein, we describe a case of de novo primary dural lymphoma (PDL) secondary to subdural empyema diagnosed after treatment for a subdural hematoma and provide a review of the relevant literature.

Illustrative Case

History of Present Illness
A 51-year-old right-handed man had been admitted to a long-term care facility with aphasia and right hemiplegia following a left putaminal hemorrhage. In June, a right subdural collection developed in parallel with headache and left hemiparesis, and the patient underwent burr hole hematoma removal at a different hospital (Fig. 1A). At that time, approximately 400 mL of a yellowish purulent fluid was observed (Fig. 1B). Culture tests were negative, but the findings were highly suggestive of infection; therefore, the patient received cefazolin for 1 week postsurgery. The patient was subsequently discharged; however, in August of the same year, fluid accumulation recurred in the subdural space, and craniotomy and drainage were subsequently performed at the previous institution (Fig. 1C). During surgery, a yellowish and cloudy fluid similar to that in the first surgery was observed, and a shunt tube, which presumably had been inserted in childhood, was removed. A culture test of the subdural fluid was performed again,
with the results again being negative. Histopathological examination of the subdural tissue showed no obvious malignant findings. Intraoperative findings strongly suggested subdural empyema, and the patient was treated with cefepime for 8 weeks. However, 2 weeks after the completion of antimicrobial treatment, subdural effusion recurred, and another craniotomy was performed in November of the same year. Intraoperative findings were the same as before, and the subdural space was well irrigated. Culture of the effusion was negative. Postoperatively, the patient was treated with vancomycin and cefepime for 8 weeks. After approximately 1 month of rehabilitation, he was discharged to his former facility.

Thereafter, periodic outpatient imaging follow-up was performed without any sign of recurrence until January 2 years later, when a subdural collection recurred. The patient was subsequently referred to our hospital in April of the same year (Fig. 1D). Since the patient was asymptomatic at the time of referral, we initially chose to perform only observation. However, in October, he was admitted to our hospital because of the development of left hemiparesis and insomnia due to increased subdural effusion, for decompression via burr hole drainage.

**Past Medical History**

The patient had a prior history of hydrocephalus, and a subdural subarachnoid shunt had been placed at another hospital when the patient was 9 months of age. When he was 45 years old, he had undergone a craniotomy at another hospital for hypertensive left putaminal hemorrhage. Physical examination revealed E4V4M6 on the Glasgow Coma Scale, mild motor aphasia, mild motor apraxia, and mild left hemiparesis. Manual muscle strength assessment was 5−/5. Laboratory test findings revealed white blood cells of 5300/µL and C-reactive protein of 0.90 mg/dL. No other abnormalities suggestive of any organ damage were observed. Serum virology revealed Epstein-Barr virus (EBV) viral capsid antigen (VCA) immunoglobulin A (IgA) negative, EBV VCA IgG negative.

**Imaging Findings**

Computed tomography (CT) revealed a right subdural effusion with midline shift (Fig. 2A). Magnetic resonance imaging (MRI) revealed contrast effect of the capsule of fluid, with no obvious diffusion decrease in the content of the reservoir (Fig. 2B and C).
Postadmission Course
Although subdural empyema recurrence was strongly suspected based on the patient’s clinical course, no imaging findings suggestive of active abscess formation were demonstrated. In any case, the decision was made to drain the contents via perforation for decompression and diagnosis.

Intraoperative Findings
Perforation of the hematoma membrane, identified just below the dural incision, produced a vigorous gush of serous yellow fluid. Unlike the turbid contents observed during the previous surgery (Fig. 2D), no foul odor or other obvious signs of infection were observed. The fluid content, hematoma extract, and dura specimen were all submitted for pathological and culture tests. Postoperatively, the patient showed rapid improvements in left hemiparesis and impaired consciousness.

Pathology Findings
Cytology was class V. Pathological examination of the dura/hematoma adventitia revealed a cluster of large, highly atypical lymphocytes along the capsule on hematoxylin and eosin (H&E) staining (Fig. 3A and B), which were diffusely positive for CD20 (Fig. 3C) and had a remarkably high Ki-67 labeling index (Fig. 3D). Considering the absence of small lymphocytes, plasma cells, or follicle structures that typically manifest in immune-related responses, the final pathological diagnosis of B-cell lymphoma (BCL; diffuse large BCL [DLBCL] suspected) was rendered. However, the absence of a discernible tumor mass in the specimen posed limitations to the definitive diagnosis, which would have otherwise been more conclusive.

Postoperative Course
Contrast-enhanced CT of the trunk showed findings suggestive of descending colon cancer, and a colonoscopic biopsy was performed. As there were no other obvious lesions on the trunk, the intracranial lesion was diagnosed as a PDL. The results of spinal fluid cytology by a simultaneously performed lumbar puncture were classified as class I. It was concluded that the PDL was confined to the subdural lesion, with no spinal fluid dissemination. After the diagnosis was confirmed, the patient was transferred to the Department of Hematology, and whole-brain radiation was administered (30 Gy/15 fractions) plus boost radiation (10 Gy/5 fractions) to the right temporal subdural space (Fig. 4A). Subsequently, surgery for descending colon cancer was performed. After radiotherapy, the subdural effusion decreased, and remission was maintained without reaccumulation (Fig. 4B and C). The patient was scheduled to receive adjuvant systemic chemotherapy from his local physician following discharge.

Patient Informed Consent
The necessary patient informed consent was obtained in this study.

Discussion
Observations
Malignant lymphomas include a subtype whose pathogenesis is linked to local inflammation caused by Helicobacter pylori or other infectious agents, similar to gastric mucosa-associated lymphoid...
tissue (MALT) lymphoma. Another subtype in which the host lymphocytes are transformed by infectious EBV or other agents to achieve pathogenesis, as in some cases of Burkitt lymphoma, has also been described. In both subtypes, pre-existing infections contribute to disease pathogenesis. The latter type is believed to involve a mechanism in which EBV-infected B cells become tumors under the influence of the surrounding inflammatory environment. Malignant lymphomas secondary to chronic inflammation, such as pyothorax, are associated with this pathogenic mechanism, with DLBCL as the most common pathology.

In our case, a definitive diagnosis of subdural empyema was difficult because the microbiological diagnosis was indefinite. However, given the yellowish viscous contents of the subdural collection, in which a foreign body (shunt tube) had been present since an early age, and the clinical history of no recurrence on imaging for more than 18 months after antibiotic treatment, it is likely that the subdural empyema and resulting chronic inflammation preceded the development of de novo dural lymphoma. Although it is not clear at what point lymphoma developed, the reappearance of subdural effusion led to surgery and a definitive diagnosis. To summarize the timeline, the lymphoma developed, the reappearance of subdural effusion led to surgery and a definitive diagnosis. In the present case, the diagnosis of dural lymphoma was made 28 months after the initial presentation of subdural empyema. The fact that the serum was negative for EBV VCA IgA and IgG and that only one EBV-encoded small RNA 1–positive cell was found in the dura and outer membrane of the hematoma in the pathology specimen suggested that the underlying pathology in this case was not an EBV infection but rather a secondary lymphoma associated with local inflammation. This suggests that the same pathogenesis as pyothorax-associated lymphoma can occur intracranially.

In the literature, multiple researchers have reported a total of 14 cases of PCNSL that were initially diagnosed as subdural hemorrhage; the characteristics of these cases are presented in Table 1. Of these 14 cases, 10 were MALT lymphoma, 2 were DLBCL, 1 was Burkitt lymphoma, and 1 was lymphoplasmacytic lymphoma. Primary dural DLBCL, as in the present case, is rare (2 of 14 cases), and there have been no reports of cases preceded by an intracranial infection. To our knowledge, this is the first report of de novo PCNSL-DLBCL developing after chronic intracranial inflammation with multiple recurrences of brain empyema. This experience suggests that it is important to consider PDL as a background pathology of chronic subdural hematoma when the history of preceding trauma is unclear, especially if there is any previous history of intracranial inflammation.

In terms of treatment, local control was achieved at the end of radiotherapy in the present case, and chemotherapy was considered. In the aforementioned series, 6 of the 10 patients with MALT lymphoma were treated with radiotherapy alone, 1 with chemotherapy alone, 2 with no additional treatment (both patients deteriorated postoperatively and deceased), and treatment was not described in 1. In addition, both DLBCL cases were treated with radiation alone, and lymphoplasmacytic lymphoma was treated with chemotherapy alone (Table 1). In other words, radiation therapy alone seems to be the most frequently chosen posttreatment option, but in lymphoma in general, there are reports that the response rate to chemotherapy is high if the pathological diagnosis is low-grade BCL. Conversely, chemotherapy plus radiation therapy is used in most cases of pyothorax-related malignant lymphoma. The question of whether patients with PDL who present with subdural hematoma exhibit distinct prognoses compared to other PDL cases remains unresolved given the scarcity of reported cases. In general, PDL can manifest as a dural mass rather than subdural hematoma. It is characterized by low-grade B-cell marginal zone lymphoma, which typically follows an indolent clinical course and demonstrates favorable treatment responses using one or two modalities.

In the current situation of this rare disease, it is advisable to consider individualized treatment plans for each case. This study is constrained by its nature as a case report. Notably, the diagnosis remains inconclusive because of the absence of a discernible tumor mass, thus posing challenges to the precise classification of lymphoma. The uncertainty persists regarding the potential utility of a larger biopsy, given that the lesion solely has a capsule-like appearance of the surrounding hematoma adventitia on enhanced MRI, without a corresponding dural mass that could provide more optimal pathological insights.

<table>
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<th>Authors &amp; Year</th>
<th>Radiological Diagnosis</th>
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<td>Present case</td>
<td>Chronic SDH</td>
<td>BCL</td>
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info = information; MGM = meningioma; RT = radiation therapy; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; Tx = treatment.
Lessons
Herein, we report a case of de novo PDL secondary to subdural empyema diagnosed after the treatment of a subdural hematoma. This is a rare case, and the mechanisms underlying its occurrence and treatment are discussed in depth. The present case suggests that in cases of subdural effusion with unclear background pathology, it is important to include dural lymphoma in the differential diagnosis and be flexible in collecting the specimen for pathological examination.

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References

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Ibayashi, Yagisawa, Kawai. Acquisition of data: Yagisawa, Koyama. Analysis and interpretation of data: Ibayashi, Yagisawa, Shirai. Drafting the article: Ibayashi, Yagisawa, Shirai, Kawata. Critically revising the article: Ibayashi, Yagisawa, Kanda, Fukuda, Shirai, Kunii, Kawai. Reviewed submitted version of manuscript: Ibayashi, Yagisawa. Administrative/technical/material support: Yagisawa, Kuroda, Lefaucheur, Kunii. Study supervision: Yagisawa, Kunii, Kawai.

Supplemental Information
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