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Cranial neurolymphomatosis and its oncologic counterparts: Case series on malignant cranial nerve neuropathies

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Abstract

Neurolymphomatosis occurs due to the infiltration of a nerve by malignant cells. Cranial neurolymphomatosis is a rare disease process associated with non-solid tumors (i.e., lymphoma, leukemia, etc.). Cranial neurolymphomatosis presents with single or multifocal neuropathy. Primary cranial neurolymphomatosis is defined as the initial presenting symptom leading to a new diagnosis of cancer. Secondary cranial neurolymphomatosis is defined as cancer progression with spread to a cranial nerve. While cranial neurolymphomatosis is a recognized cause of cranial nerve neuropathies, a myriad of other malignancies can also lead to similar clinical manifestations. This case series elucidates not only the classical presentations associated with cranial neurolymphomatosis but also introduces other oncologic entities that may compromise cranial nerve functions. A descriptive case series is presented on six patients with malignancy-related cranial neuropathy who came to a tertiary-care center from 2018 to 2022. 5/6 (83.3%) of patients presented with primary cranial neuropathy. Diffuse large B-cell lymphoma was the most prevalent malignancy observed in 3/6 (50.0%) cases. Other malignancies observed include non-Hodgkin lymphoma, monoclonal B-cell lymphocytosis, and peripheral T-cell lymphoma. The most affected cranial nerve was the trigeminal nerve in 4/6 (66.6%) individuals. Multiple cranial neuropathies were seen in 2/6 (33.3%) of patients. The most common neuroradiographic finding was a lesion to Meckel's cave. Other cranial nerves affected include the optic, facial, and vestibulocochlear nerves. Diagnostic modalities utilized included magnetic resonance imaging and ^{18}F-fluoro-2-D-glucose positron emission tomography-computerized tomography. Cerebrospinal fluid analysis for flow cytometry may also have diagnostic value in patients with increased disease burden. Treatment was guided according to individual malignancy and 2/6 (33.3%) patients achieved complete remission, 2/6 (33.3%) died within 1 year, and 1/6 (16.6%) were referred to hospice. Cranial neuropathy may be the first symptom of a neoplastic process; thus, prompt recognition and treatment may improve morbidity and mortality.

Keywords

Cranial neurolymphomatosis, peripheral neurolymphomatosis, non-Hodgkin lymphoma, T-cell lymphoma, Burkitt lymphoma, cranial nerve palsy

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Introduction

Neurolymphomatosis (NL) is the process of invasion of the endoneurium of peripheral nerves by malignant lymphocytes. It is strongly associated with non-Hodgkin lymphoma but can also be associated with other hematologic malignancies.[1] The pathophysiology is different from neurological symptoms caused by paraneoplastic, metabolic, or treatment-related effects, and it is distinct from an external compression by a mass lesion. Cranial neurolymphomatosis (CNL) is the invasion of a cranial nerve by malignant cells. When NL is the initial presenting symptom that leads to a diagnosis of malignancy, it is termed primary neurolymphomatosis. When NL is

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identified as a previously diagnosed cancer, it is termed secondary neurolymphomatosis. The definitive diagnosis requires histopathology showing malignant lymphocytic infiltration of the nerve; however, most cases are identified by a combination of imaging and clinical suspicion. Imaging findings for NL are nonspecific but would present as increased contrast uptake on ^{18}F-fluoro-2-D-glucose (FDG) positron emission tomography-computerized tomography (PET-CT).[2] The most widely used modality is magnetic resonance imaging (MRI), where NL generally appears as a diffuse thickening of the nerve with enhancement beyond the dural sleeve. Cerebrospinal fluid (CSF) studies can also be helpful in cases where malignant cells are identified. Treatment may include systemic chemotherapy, and local radiation, but ultimately can progress to invading the CSF and central nervous system (CNS) by blood–brain barrier breakdown.[3] Primary neurolymphomatosis is frequently accompanied by a latency period in the diagnosis of the disease. However, accurate identification of primary NL can improve survival, due to earlier initiation of systemic treatment for the underlying cancer. NL is a rare manifestation of malignancy, and its recognition is essential to make an accurate diagnosis. Limited cohorts of isolated CNL have been reported in the past. Thus, we present a case series of six individuals with CNL that demonstrate the diversity in associated malignancies, presenting symptoms, and treatment.

The spectrum of malignancies affecting the cranial nerves extends beyond the confines of CNL. While neurolymphomatosis is a well-documented etiology, other malignancies, from primary brain tumors to systemic cancers, can exhibit cranial nerve neuropathies due to direct invasion, paraneoplastic syndromes, or metastatic spread. Recognizing this diverse oncologic landscape is crucial for accurate diagnosis and timely intervention.

Case presentation

Six cases of malignancy-related cranial neuropathies are reported that were diagnosed and treated at UMass Memorial Medical Center, a tertiary-care center in Worcester, Massachusetts, USA. All cases were diagnosed between 2018 and 2022. Information reported includes age, demographics, malignancy type, diagnostic modality, primary or secondary cranial neuropathy, neurological deficits, cranial nerve involved, time to onset from cancer diagnosis, treatment, and outcomes. Primary cranial neuropathy is defined as neurological manifestations due to cranial nerve infiltration as the first manifestation of malignancy. Secondary cranial neuropathy refers to cranial nerve infiltration and neurological symptoms after the diagnosis of cancer. Figure 1 provides neuroimaging findings seen in our cohort. Table 1 provides an overview of case characteristics, diagnostics, treatment, and outcomes.

Case 1. A 53-year-old woman presented with a 1-month history of fever, night sweats, 20-lb weight loss, progressive shortness of breath, and neck swelling. Physical examination was significant for bulky cervical lymphadenopathy with nasopharyngeal and oropharyngeal airway narrowing due to mass effect. The patient underwent a lymph node (LN) biopsy of the right cervical LN revealing a lymphoma with a diffuse growth pattern composed of predominantly large lymphoid cells with relatively open chromatin and prominent nucleoli. The lymphoma cells were CD20, CD30, Epstein Barr virus (EBV), and BCL-2 positive. The *Ki67* proliferative index was approximately 80% in lymphoma cells.[4] Fluorescence in situ hybridization (FISH) was significant for BCL-2, BCL-6, and C-MYC negative rearrangement.[5] Flow cytometry showed a 15% monoclonal lambda-restricted B-cell population that is CD5 and CD10 negative. The patient was started on rituximab, etoposide, prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin (R-EPOCH) chemotherapy regimen and completed two cycles.

The patient presented to the hospital approximately 2 months after the initial diagnosis with acute onset blurry vision and sensation changes to the left side of the face. Neurological examination was significant for a left abducens nerve palsy and numbness on the left side of the face consistent with a left abducens and trigeminal nerve palsy. An MRI of the brain with and without gadolinium contrast revealed effacement of the left Meckel's cave and thickening of the proximal aspect of the mandibular division of the left trigeminal nerve. These findings were consistent with secondary CNL. A subsequent goal of care discussion was held, and the patient opted for hospice care and expired 1 month later.

Case 2. A 68-year-old male presented to the neurology clinic with a 1-month history of persistent facial numbness. Initial physical examination was significant for numbness and tingling to light touch, vibration, and temperature on the right side of the face involving all three cardinal branches (VI, VII, and VIII) of the trigeminal nerve. An MRI of the brain with and without contrast was obtained revealing enhancement along the right Meckel's cave. An MRI of the orbit, face, and neck revealed enhancement of the right medial pterygoid and masseter muscle. Given the concern for a possible neoplastic process, a PET scan was obtained revealing FDG uptake along the right trigeminal nerve. The patient subsequently underwent a biopsy of the right pterygopalatine fossa, and right medial pterygoid revealing lymphoma involving a large nerve with both intra- and perineural involvement. Immunohistochemistry revealed CD20, PAX5, CD10, and BCL6-positive neoplastic lymphoid cells. And negative for BCL2, MUM1, cyclin D, and CD30. C-MYC stains >95% of the cells, and the *Ki67* index was high (>90%). In situ hybridization for EBV-encoded RNA (EBER) was positive. Concurrent FISH studies demonstrated MYC rearrangement without BCL2 and BCL6 rearrangement. These findings were consistent with an EBV-positive high-grade B-cell lymphoma of germinal

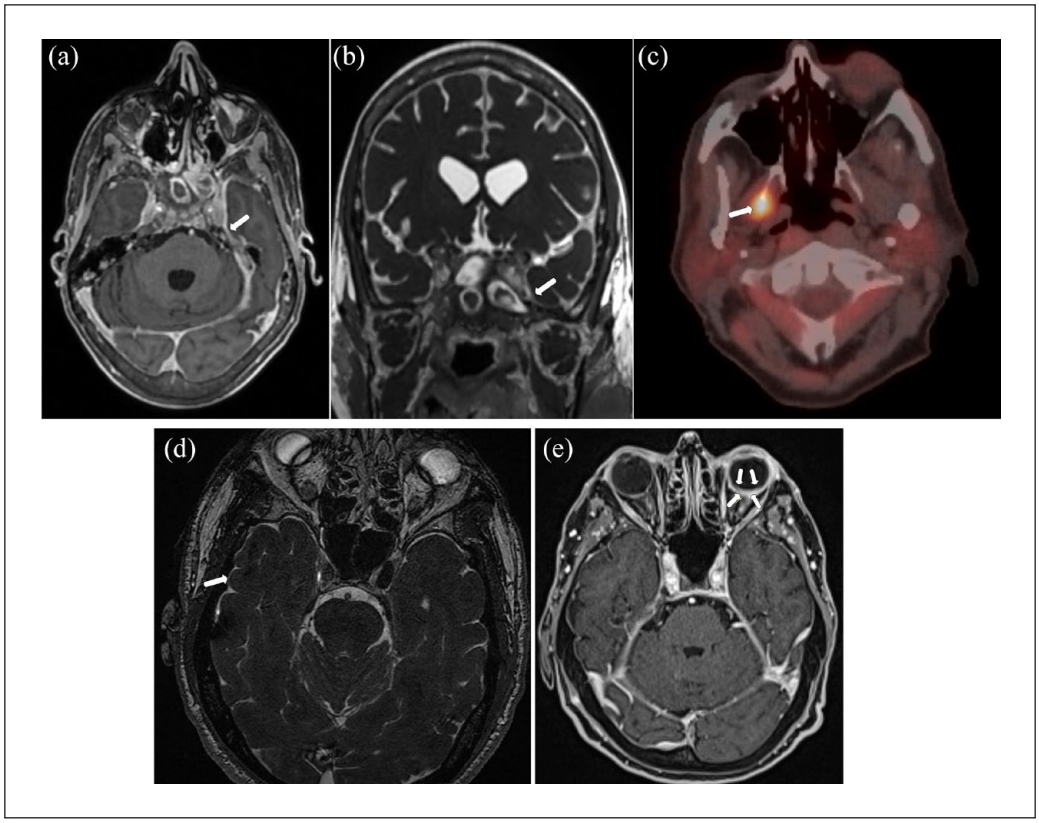

Figure 1. Neuroimaging findings reveal cranial neurolymphomatosis. (a) Case one: MRI axial T1 contrast-enhanced (C+) sequence showing effacement of Meckel's cave. (b) Case one: coronal T2 sequence reveals perineural invasion of the trigeminal nerve. (c) Case two: area of focal FDG uptake in the right 5th cranial nerve. (d) Case four: MRI FIESTA sequence shows focal enhancement of the right oculomotor nerve. (e) Case six: MRI T1 C+ sequence shows focal enhancement on the left globe.
FIESTA: fast imaging employing steady-state acquisition.

center B-cell origin. CSF studies with flow cytometry confirmed the presence of lymphoma with neoplastic cells.

The patient received one round of cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone (hyper-CVAD). Subsequently, the patient was treated with one round of high-dose (HD) methotrexate (MTX), and two rounds of rituximab, cyclophosphamide, doxorubicin hydrochloride, Oncovin (vincristine), and prednisolone (R-CHOP). Despite treatment, the patient expired 1 year later.

Case 3. A 90-year-old woman presented with a 1-month history of left-sided facial weakness. A neurological examination revealed facial nerve paresis in the distribution of the mandibular branch. Palpable LNs were appreciated in the left cervical LN chain. Furthermore, a palpable mass was appreciated in the left cheek. A computerized tomography (CT) scan of the facial bones, and sinuses revealed a soft tissue mass in the left cheek in the region of the nasomaxillary fold extending posteriorly to involve the maxillary sinus, left orbit, and infratemporal fossa. A PET scan was obtained revealing increased FDG uptake in the left cheek and the left neck. A fine-needle aspiration was completed revealing malignant cells. The patient was diagnosed with non-Hodgkin lymphoma opted to forego chemotherapy and was discharged to hospice.

Case 4. A 65-year-old male presented with a 2-week history of progressive right-sided facial weakness, fever, and chills. Initial neurological examination was significant for a right-sided Bell's palsy, mild bilateral dysmetria on finger-nose-finger testing, and positive Romberg test. An MRI of the brain with fast imaging employing a steady-state acquisition (FIESTA) sequence was completed which revealed enhancement along the bilateral cranial nerves III, VI, VII, and VIII CSF analysis revealed elevated protein >333 mg/dL (0–35) and 1ymphocytes 113 cells/m^3 (0–10). Serum flow cytometry revealed lymphoma cells that are CD19+, CD20+, CD10+, CD5−, and kappa negative. The lymphoma cells comprised 1.3% of total nucleated cells. Flow cytometry results were consistent with non-CLL type monoclonal B-cell lymphocytosis. A whole-body PET scan was completed showing a 1.1 cm pleural-based nodular opacity in the right lower lobe with moderate FDG activity. The patient

Table 1. Clinical characteristics observed in the six reported cases of malignant cranial neuropathy.

Case no.	Age	Gender	Primary/ secondary	Cranial nerve deficit(s)	Imaging finding(s)	TTO[a]	Malignancy	Management	Outcomes
1	53	F	Secondary	Left CN V	MRI: effacement of left Meckel's cave and thickening of the left trigeminal nerve. Consistent with perineural spread	2	DLBCL	R-EPOCH	Deceased 4 months after starting treatment
2	68	M	Primary	Right CN V	MRI: enhancement of the right Meckel's cave. PET: FDG uptake in the right CN V.	0	DLBCL	Hyper-CVAD, HD MTX, R-CHOP	Deceased 13 months after starting treatment
3	90	F	Primary	Left CN VII	CT: soft tissue mass in the left maxillary sinus, left orbit, and infratemporal fossa. PET: FDG uptake in the left cheek and neck	0	NHL	Supportive	Hospice care
4	65	M	Primary	Bilateral CN III, VI, VII, VIII	MRI: bilateral enhancement of cranial nerves III, VI, VII, and VIII	0	Monoclonal B-cell lymphocytosis	IVMP	Remission at 1-year follow-up
5	64	M	Primary	Left CN V	MRI: minor enhancement on the root entry zone of the left trigeminal nerve	0	Peripheral T-cell lymphoma	EPOCH	Continuing chemotherapy regimen at 1-year follow-up
6	75	M	Primary and secondary	Primary left CN II, globe, and secondary bilateral CN V	MRI: mild thickening and enhancement of the left globe posterior to the retina, and optic nerve. Second MRI: enhancement of the bilateral Meckel's cave. PET: FDG uptake in the left posterior globe	0	Retinal DLBCL	MTX	Remission at 1-year follow-up

TTO[a]: Time to symptom onset (in months) from a cancer diagnosis.
CN: cranial nerve; DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; R-EPOCH: rituximab, etoposide, prednisolone, oncovin, cyclophosphamide, hydroxydaunorubicin; HD MTX: high-dose methotrexate; Hyper-CVAD: cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin (vincristine), and prednisolone; IVMP: intravenous methylprednisolone; FDG: fluorodeoxyglucose; PET: positron emission tomography; TTO: Time-to-onset.

was treated with high-dose intravenous methylprednisolone for 5 days and a prednisone taper. The patient's Bell palsy and dysmetria had significantly improved. The patient was subsequently discharged with close oncology, pulmonology, and neurology follow-up. A repeat MRI brain 3 months later revealed improvement in the enhancement of the bilateral cranial nerves. A repeat CT scan of the chest revealed a stable pulmonary nodule. The patient continues to remain in remission at the 1-year follow-up.

Case 5. A 64-year-old male presented with a 2-day history of double vision and facial droop. The patient described waking up from a nap with double vision and electric-shock-like pain when brushing his teeth. Initial neurological examination was significant for moderate numbness and tingling on the left side of the face with intermittent sharp shooting pain. Initial laboratory serum testing was significant for an elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 1000. A liver biopsy was completed revealing CD3+ T cells that co-express CD4 and show aberrant loss of CD5 and CD7 expression, consistent with neoplastic T cells. There was co-expression of perforin and focal TIA-1 by a subset of lymphoma cells. The *Ki67* proliferation index was at least 50%. In situ hybridization for EBV-encoded RNA (EBER) is negative as well as for cytomegalovirus (CMV). These findings are consistent with liver involvement by peripheral T-cell lymphoma. A bone marrow biopsy with immunohistochemistry revealed many CD3-positive T cells. CD5 and CD7 expressions were absent in T cells. CSF analysis with flow cytometry revealed an atypical population of CD3+, CD4+, CD8−, CD5−, and CD7+ T cells. An MRI brain was completed revealing minor enhancement on the root entry zone of the left trigeminal nerve. The patient was diagnosed with peripheral T-cell lymphoma. The patient started on an EPOCH chemotherapy regimen. Rituximab was not given as the patient was EBV negative.

Case 6. A 75-year-old male presents with a 2-week history of blurry vision in the left eye. The initial fundoscopic examination was consistent with intravitreal hemorrhage and uveitis. Visual acuity was 20/60 in the left eye and 20/30 in the right eye. With concern for an infectious process, the patient was started on foscarnet. His symptoms did not improve over the next 2 months and his visual acuity worsened. He underwent vitrectomy and pathological findings including focal involvement of diffuse large B-cell lymphoma (DLBCL). CSF studies were significant for elevated protein 58 mg/dL (0–35). CSF flow cytometry revealed many lymphocytes which were CD19+ and CD20+. An MRI of the brain revealed mild thickening and enhancement of the left globe posterior to the retina and optic nerve. A PET scan revealed focal FDG uptake at the posterior left globe, thoracic lymphadenopathy, and splenomegaly. The patient was initially treated with high-dose MTX. Six months later, the patient developed bilateral numbness and tingling along the maxillary and mandibular branches of the trigeminal nerve. A repeat MRI of the brain revealed enhancement of the bilateral Meckel's cave and left globe. Radiation therapy was administered to the patient with subsequent resolution of symptoms. The patient continues to remain in remission at the 1-year follow-up.

Discussion

Six cases of malignancy-related cranial neuropathy have been presented with varying etiologies, presentation, and cranial nerve involvement. Malignancy-related cranial neuropathy remains one of the rarest clinical manifestations of lymphomas of the nervous system. The vast majority of cases occur due to large B-cell non-Hodgkin lymphoma (NHL), with an incidence of 0.2% across all NHLs.[6] Within our case series, cranial neuropathy occurred due to NHL in one patient, and 3/6 cases occurred due to DLBCL, and one due to T-cell lymphoma. In an NHL autopsy study, peripheral nerve involvement was observed in 40% of patients.[7] Therefore, malignancy-related cranial neuropathy is likely to occur asymptomatically in the vast majority of patients. Involvement of multiple peripheral nerves is common; however, singular nerve involvement is possible. Within our series of cases isolated, cranial nerve involvement was seen in 4/6 (66.6%) patients. Cases 4 and 6 had primary cranial neuropathy in more than one cranial nerve. The pathophysiology of malignancy-related cranial neuropathy is believed to involve focal infiltration within the nerve that causes demyelination, microglia infiltration, and axonal degeneration.[8] Interestingly, while the majority were secondary cranial neuropathy, occurring after a known cancer diagnosis, the potential for primary cranial neuropathy, where the neurological symptoms are the maiden sign of malignancy, remains a striking aspect of some cases. Such primary manifestations emphasize the clinical acumen required to detect and diagnose this rare entity in its earliest stages.

The clinical presentation of malignancy-related cranial neuropathy varies greatly based on the infiltrated cranial nerve and the severity of the infiltration. Cranial neuritis can present with or without pain. Disease progression is often insidious with progression from months to years.[1] The most used diagnostic modality includes MRI and FDG-PET/CT. MRI often shows focal nerve encasement or enhancement on contrast-enhanced sequences, significant for an infiltrative process.[9] The definitive diagnosis is often established postmortem on autopsy. Of all diagnostic tests, MRI is the most readily available and of the greatest clinical utility. The diagnostic yield for MRI and PET-CT is 84% and 77%, respectively.[10] CSF analysis with flow cytometry studies may also be beneficial in determining the malignancy, as well as assessing for CNS penetration. However, in patients with limited neurological manifestations, large-volume or repetitive CSF studies may be required.[11]

There is currently no standardized treatment for NL. Treatment often involves a combination of chemotherapy and radiotherapy. Radiation therapy has a limited role in multifocal NL due to a wide radiation field. In focal NL, limited-field radiotherapy can be very effective. High-dose MTX or cytarabine is often used due to its CNS penetrating effect.[12] In our series, 4/7 (57.1%) of the patients received systemic chemotherapy. The choice of chemotherapy is best determined based on the underlying malignancy.

Information related to the overall survival of patients with NL is sparse. In our cohort, one patient was deceased at 4 months and another at 13 months despite treatment. However, three patients were able to obtain remission with a 48-month survival proportion of 57.1%. A larger cohort analysis of 50 patients had a 36-month survival proportion of 24%.[13] The outcomes and survival rate are likely closely related to the underlying malignancy and early diagnosis as well as prompt treatment in those with malignancy-related cranial neuropathy. Previous cohort studies evaluating malignancy-related neuropathy had individuals with peripheral and cranial nerve involvement. Thus, a large cohort analysis of patients with only malignancy-related cranial neuropathy is needed to assess long-term outcomes.

Our case series highlights the importance of recognizing cranial neuropathy as an initial presenting feature of malignancy. 5/6 (83.3%) of patients had neurological manifestations secondary to cranial neuropathy as the initial presenting symptom of a neoplastic process. Trigeminal nerve involvement was most prevalent in our cohort (5/6, 83.3%); however, involvement of other cranial nerves including the oculomotor, facial, and vestibulocochlear nerves was also observed. Therefore, an accurate initial neurological evaluation including an MRI ideally with a FIESTA sequence should be completed to evaluate patients with high suspicion of cranial neuropathy.[14,15] Only case four from our case series completed a FIESTA sequence MRI. Early recognition of a malignant process may be beneficial in morbidity and mortality. As this series consists of only six cases from a single tertiary-care center, our observations may not generalize to broader populations or different clinical settings. Larger, multi-center studies would offer more comprehensive insights. Though the cases underwent multiple diagnostic modalities, the absence of uniform diagnostic criteria across all patients might influence the observed patterns. In addition, given the rarity of NL, even specialized imaging may not have the ideal sensitivity or specificity to detect it. Other limitations include the lack of multi-year long-term follow-up.

Conclusions

A case series of six patients with CNL and other malignancy-related cranial neuropathies is described. 5/6 (83.3%) of patients presented with cranial neuropathy as the primary symptom of the malignancy. An MRI with a FIESTA sequence may allow for better visualization of the cranial nerves and their origin when assessing for malignant neuropathy. In our cohort, the survival proportion at 48 months was 57.1%. In patients with cranial neuropathy, prompt neurological evaluation, including imaging, is important in the early recognition of a neoplastic process and can improve morbidity and mortality outcomes.

Article note

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Author contributions

BSS completed the literature review, drafted the initial manuscript, generated illustrations/figures, and tables, provided intellectual verification of the topic, and edited the final manuscript. AB drafted the initial manuscript. VK provided intellectual verification on this topic. All authors reviewed the final draft of the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Ethics approval

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article. Written informed consent from the subject's legally authorized representative for the publication of this case report was obtained for case no. 1 and 2 (deceased subjects).

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