Primary Cauda Equina Lymphoma Treated with CNS-Centric Approach: A Case Report and Literature Review

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Abstract: Primary cauda equina lymphoma is an extremely rare entity previously documented in only 24 reported cases. Primary cauda equina lymphoma represents a subtype of neurolymphomatosis, which occurs when lymphoma cells with neurotropism infiltrate and destroy peripheral nerves, spinal nerve roots, nerve plexuses and cranial nerves. The cauda equina is an anatomic structure located in the lower part of the spinal canal consisting of multiple lumbar and sacral nerve roots. Herein, we report a unique case of primary cauda equina diffuse large B-cell lymphoma presenting as a tumor mass in the lower spinal canal, which was treated with a CNS-centric treatment approach followed by autologous hematopoietic stem cell transplantation.

Keywords: primary cauda equina lymphoma, neurolymphomatosis, diffuse large B cell cauda equina lymphoma, MATRIX chemoimmunotherapy, autologous stem cell transplant

Introduction

In rare instances, malignant lymphoma cells can be discovered as primary lesions originating within the spinal cord, and even more rarely, within the cauda equina itself. The cauda equina is an anatomic structure in a crowded lower spinal canal consisting of multiple lumbar and sacral nerve roots. Primary cauda equina lymphoma (PCEL) presents as a primary lesion within the cauda equina, and has only been reported in a limited number of case reports. PCEL appears to comprise less than 1% of neurolymphomatosis cases.

Neurolymphomatosis is a rare lymphomatous manifestation in which lymphoma cells with neurotropism infiltrate and destroy peripheral nerves, spinal nerve roots, nerve plexuses and cranial nerves. Histologically, the majority of neurolymphomatosis cases involve B cell lymphomas, with previous studies documenting frequencies of B-cell involvement as high as 82% and 97.5%.

Occurring less frequently, T-cell lymphomas have been found to range anywhere from 2.5% to 10% of cases. Typically presenting due to secondary involvement from systemic lymphoma, primary neurolymphomatosis is extremely rare. PCEL appears to comprise less than 1% of neurolymphomatosis cases. We report a unique case in which diffuse large B-cell lymphoma involved multiple nerve roots in the cauda equina, presenting as a large tumor occupying the lower spinal canal. Moreover, we describe and highlight the unique treatment approach incorporated in the case of our patient.
Case Presentation
A 55 year-old Asian female patient presented to an outside facility with complaints of tingling, numbness, and significant pain radiating into both lower extremities. Her pain was accompanied by loss of bowel and bladder function as well as significant weakness in both legs resulting in a loss of sensation and mobility. The patient was referred to our institution for further evaluation.

Figure 1 (A) Gadolinium enhanced sagittal and coronal TI MRI showing diffuse involvement of cauda equina with encasement of conus medullaris (arrows). (B) Staging whole-body 18F-FDG PET-CT coronal and sagittal views showing hypermetabolic mass in the cauda equina and lumbar nerve root sleeves (arrows).

Figure 2 (A) Pathology examination by H&E staining revealing diffusely infiltrating large atypical lymphocytes dissecting through the nerve bundles (arrow indicating residual nerve). IHC studies showed that the neoplastic lymphocytes were positive for (B) CD20, (C) BCL2, (D) BCL6, (E) MUM1, (F) with a high proliferate rate (>90%) by Ki-67.

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in multiple falls, inability to ambulate and subsequent wheel-chair dependency. She further complained of consistent radicular pain radiating around her abdomen. Initial magnetic resonance imaging (MRI) of the lumbar spine identified a homogeneously enhancing mass diffusely infiltrating the cauda equina and filum terminale, superiorly encasing the conus medullaris (Figure 1A). PET-CT scan of the whole body revealed a markedly hypermetabolic tumor occupying the spinal canal and nerve root sleeves from T12 to S1 with no evidence of the disease outside the spine (Figure 1B).

The patient underwent L1-L4 lumbar laminectomy with biopsy of the tumor. Hematoxylin and eosin (H&E) sections of the tumor demonstrated diffusely infiltrating large atypical lymphocytes encasing the lumbar nerve (Figure 2A). Immunohistochemical (IHC) studies showed that the neoplastic lymphocytes were positive for CD20, CD79a, BCL6, BCL2, and MUM1 (Figure 2B–E); negative for CD10, TdT, cyclin D1, and MYC. The proliferative rate by ki-67 was also high (>90%) (Figure 2F). Fluorescence in situ hybridization (FISH) analysis from resected tissue was negative for MYC and BCL2 rearrangement, but positive for BCL6 rearrangement in 80% of nuclei. Cerebrospinal fluid (CSF) cytology was positive for lymphoma cells. These findings were consistent with activated B cell subtype of diffuse large B-cell lymphoma (ABC-DLBCL). A bone marrow aspirate and biopsy were negative for lymphomatous involvement.

The patient was subsequently initiated on systemic therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with mid-cycle high-dose methotrexate (HD-MTX). After completing 5 cycles of treatment, restaging MR of the spine and PET-CT scans revealed some residual hypermetabolic abnormalities within the spine despite improved resolution of the spinal lesion. It was at this time that the patient presented to our department for further management and evaluation for potential autologous stem cell transplant. Although her neurological status seemed to be somewhat improved in her lower extremities, the patient continued to endorse sensory symptoms in the lower extremities and abdomen as well as significant weakness in her right lower extremity. These clinical findings in combination with restaging PET scan indicated a partial response to previous treatment with R-CHOP and HD-MTX.

She was then initiated on consolidation treatment with 2 cycles of methotrexate, cytarabine, thiopeta, and rituximab (MATRIX) chemoimmunotherapy due to previously reported success of MATRIX therapy in patients with primary central nervous system lymphoma (PCNSL). Following the first cycle of MATRIX, the patient reported significant improvement in symptoms as her legs felt much stronger and she was finally able to ambulate on her own with the assistance of a walker. Restaging following MATRIX therapy with PET-CT, MRI of the brain, and MRI of the spine revealed complete resolution of the original lesion with no evidence of disease elsewhere in the body (Figure 3). She then underwent high-dose Bis-chloroethyl nitrosourea (BCNU) plus thiopeta followed by autologous hematopoietic stem cell transplantation (auto-SCT). Restaging after auto-SCT with MRI of the thoracic and lumbar spine at day +100 continued to reveal no evidence of disease. She was then initiated on maintenance therapy with Ibrutinib 560 mg daily. At 18 months following the initial diagnosis, the patient has remained in complete remission and her neurological status has greatly improved with regaining of her right lower extremity strength with the help of intensive physical therapy.

**Discussion and Literature Review**

The clinical and pathologic findings for our patient are most consistent with PCEL with CSF involvement. Her presenting neurological findings fit the classical presentation of cauda equina syndrome. Radiologic review of her imaging scans from the time of initial presentation did not show any evidence of intramedullary involvement of the spinal cord, but they did reveal a mass encasing multiple nerve roots in the cauda equina. Unlike typical neurolymphomatosis which most commonly represents a challenging diagnostic entity due to patchy nerve involvement requiring multiple biopsies and investigations over time, our patient presented with a solid tumor due to lymphomatous involvement of multiple nerve roots in the cauda equina region in a tight spinal canal. This unique presentation, in contrast to most cases of neurolymphomatosis, allowed for a more expedient diagnosis and prevented any delays in treatment. The pathologic findings in our case were consistent with activated B cell subtype of DLBCL associated with BCL6 translocation. The immunophenotype is similar to that of PCNSL; there was positive expression of CD20, BCL6, and MUM1.

Our patient was initially treated with R-CHOP with mid-cycle HD-MTX achieving a partial response. Under our care, she was further treated with two cycles of MATRIX resulting in complete remission. Although
radiation therapy was originally offered to the patient as an alternative consolidation therapy, the patient declined any radiation therapy and elected to undergo high-dose chemotherapy followed by auto-SCT. Since it is well known that PCNSL is more amenable to cure at initial diagnosis that in the relapsed/refractory setting, we believed that it was critical for our patient to receive CNS penetrating agents to ensure that the entire CNS was permeated with therapeutic agents. Because we felt that she did not receive good CNS coverage during her initial induction treatment, it was decided that she receive consolidation therapy with two cycles of MATRIX therapy. She was further consolidated with high-dose BCNU and Thiotepa chemotherapy followed by auto-SCT. She has remained in complete remission following the transplant. We decided to put her on maintenance Ibrutinib as her lymphoma was aggressive with significant neurological impacts. Ibrutinib has previously shown significant therapeutic efficacy in ABC-DLBCL and PCNSL with excellent CNS penetration. It is also pertinent to emphasize the importance of the role of intensive physical therapy, which tremendously helped our patient during her recovery.

Our medical literature review identified 25 PCEL patients (Table 1) with a median age of 55.5 years (range 11–79) at the time of diagnosis and a 3:2 male to female predominance. Of those cases that describe lymphoma type, 91% (22/24) classify as B-cell lymphoma whereas only 9% (2/24) describe lymphomas that are T-cell in origin. Diffuse large B-cell lymphoma clearly appears to be the most common subtype as it comprises 77% of those lymphomas that are B-cell in nature and 72% of all PCEL cases in general (17/24). It is also worth noting that over half of patients presented with a mass-like lesion in the cauda equina region on imaging of the spine (62.5%, 15/24) and CSF involvement by lymphoma was reflected on cytology in more than half of cases when lumbar puncture was performed (52.6%, 10/19). Of the 23 cases which included descriptions of treatment, the most common

Figure 3 Follow up MRI (A) and PET-CT (B) after chemotherapy showing complete resolution of the hypermetabolic cauda equina lesion. Linear FDG uptake in the posterior lumbar dura (arrows) is postoperative in nature.
| Reference  | Age/ Sex | Pathology | CSF Involvement (Cytology) | Mass-Like Lesion | Treatment                                                                 | Outcome               |
|-----------|----------|-----------|---------------------------|-----------------|---------------------------------------------------------------------------|-----------------------|
| Nakashima 2014 | 59/M     | DLBCL     | Yes                       | Yes             | Radiotherapy, intravenous methotrexate                                     | Alive; 1 year         |
| Mauney 1983 | 68/F     | DLBCL     | Yes                       | Yes             | Radiotherapy                                                              | Alive; 3 months       |
| Toner 1989 | 59/M     | DLBCL     | Yes                       | No              | Radiotherapy, intrathecal methotrexate, intravenous cyclophosphamide       | Alive; 2 years         |
| Klein 1990 | 29/F     | B-cell lymphoma | No                         | Yes             | Tumor resection                                                           | Died; 5 weeks          |
| Knopp 1994 | 69/F     | N/a       | N/a                       | No              | N/a                                                                       | N/a                   |
| Ooi 1996  | 16/M     | T-lymphoblastic lymphoma | N/a                  | Yes             | Radiotherapy, intrathecal methotrexate, intravenous methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone | Died; 8 months         |
| Zagami 2003 | 71/F     | DLBCL     | Yes                       | No              | Intra-thecal methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone | Died; 16 months        |
| Kumar 2005 | 60/M     | No        | No                        | No              | IVIG, Rituximab                                                           | Alive; 6 months        |
| Tajima 2007 | 67/F     | DLBCL     | No                        | Yes             | Radiotherapy and intrathecal methotrexate, IVIG, intravenous carboxplatin | Alive; 3 years         |
| Morita 2009 | 67/M     | NK/T-cell lymphoma | N/a                  | Yes             | Radiotherapy, surgical resection, and etoposide                            | Died; 14 months        |
| Teo 2012  | 58/M     | DLBCL     | No                        | Yes             | Radiotherapy, steroids, and intravenous chemotherapy                       | Alive; 2 years         |
| Iwasaki 2012 | 69/M     | DLBCL     | N/a                       | No              | Radiotherapy and intravenous methotrexate                                  | Died; 1.5 years        |
| Nishida 2012 | 47/M     | DLBCL     | Yes                       | Yes             | Radiotherapy, intravenous methotrexate and cytarabine, and intrathecal methotrexate, cytarabine, prednisone | Alive; 1.5 years        |
| Broen 2014 | 75/F     | DLBCL     | No                        | No              | Oral dexamethasone                                                        | Died; 10 months        |
| Broen 2014 | 71/F     | DLBCL     | No                        | No              | Intravenous doxorubicin, vincristine, cyclophosphamide, prednisone, and rituximab, and intrathecal methotrexate. | Alive; n/a             |
| Shin 2016  | 79/F     | DLBCL     | N/a                       | Yes             | Radiotherapy and chemotherapy                                             | Alive; N/a             |
| Belcastro 2016 | 47/M     | DLBCL     | No                        | Yes             | Intravenous steroids, intrathecal methotrexate, cytarabine, and rituximab | Died; 2 months         |
| Giobbi 1999 | 30/F     | DLBCL     | Yes                       | No              | Radiotherapy, intrathecal methotrexate, cytosine arabinoside, and hydrocortisone | Alive; 1 year         |
| Khong 2008 | 16/M     | DLBCL     | No                        | Yes             | Radiotherapy, intravenous dexamethasone, cyclophosphamide, cytarabine, doxorubicin, leucovorin, methotrexate, vincristine, rituximab | Alive; 1 year         |

(Continued)
method of treatment appears to be both chemotherapy and radiation (56.5%), followed by chemotherapy (30.4%), and lastly radiation (4.3%), tumor resection (4.3%), and oral steroids (4.3%). Similar to the standard treatment of lymphoma with CNS involvement, the majority of chemotherapy regimens in PCEL patients included CNS penetrating agents, including high dose methotrexate and cytarabine. The death rate at the time of publication in this review appears to be 34.8% (8/23). Of those patients that survived longer than a year, the large majority were treated with systemic chemotherapy incorporating CNS penetrating agents (85.7%, 12/14). Our case appears to be the first to incorporate MATRIX therapy for CNS penetration as well as the only report to include auto-SCT as part of the treatment for PCEL.

Conclusion

In conclusion, PCEL is a rare, yet frequently aggressive lymphoma that can manifest as a mass lesion in the lower spinal canal. The congregation and conglomeration of multiple nerve roots involved by neurolymphomatosis in a tight anatomical space helps facilitate a proper diagnosis and prevents delays in treatment. We propose that PCEL should be treated like PCNSL, with regimens consisting of CNS-penetrating agents. CNS-penetrating high-dose chemotherapy followed by auto-SCT should be considered in eligible patients.

Ethics and Consent

Written informed consent was obtained from the patient for the publication of this manuscript and any accompanying images. Institutional approval was not required for publication.

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Disclosure

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