Primary diffuse large B-cell lymphoma of the CNS: a rare case of spontaneous remission

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Practice points

- We present a case report of a patient with primary CNS lymphoma with no neurological symptomatology, who spontaneously went into a durable remission.
- Patients with immunocompromise such as HIV patients, patients on immunosuppressive agents and elder patients with immune senescence are at higher risk for Epstein-Barr virus positive lymphomas.
- Lymphomas in immunocompromised patients may spontaneously go into remission with improvement in immune function.
- Care should be taken to identify elder immunocompetent patients with Epstein-Barr virus positive primary CNS lymphoma who might be a candidate for observation rather than immediate therapy for their newly diagnosed lymphoma.

There is no consensus on the optimal therapy for primary CNS lymphoma. Conventional treatment modalities include chemotherapy and radiation therapy, which carry significant risks of morbidity and mortality. In systemic lymphomas, there are situations where non-Hodgkin lymphomas have resolved spontaneously. We now report the case of a nonimmunocompromised patient with primary CNS lymphoma who underwent a spontaneous remission with a durable response. This case suggests that not all patients with primary CNS lymphomas require aggressive treatment with chemotherapy and radiation therapy.

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Primary CNS lymphoma (PCNSL) is defined as a lymphoma presenting in the eye, brain or spinal cord in the absence of systemic lymphoma, and about 95% of these are diffuse large B-cell lymphomas [1]. The most common symptoms, which often span weeks or months, are focal deficits, personality changes and increased intracranial pressure. Once considered a rare tumor, accounting for less than 1% of all systemic non-Hodgkin's lymphomas, its incidence has increased since the 1970s [2]. The increased incidence in immunosuppressed patient populations can be attributed to the spread of HIV and prevalent use of immunosuppression agents in patients with organ transplants or autoimmune disorders. The reason for the increased frequency of the disease in immunocompetent individuals remains unclear, and may be due to better detection and diagnosis rather than true increase in the incidence of the tumor.

Spontaneous regression of a malignant tumor is highly unusual but this phenomenon is encountered on some occasion. This clinical condition is estimated to occur in 1:60,000–1:100,000 patients with cancer and the phenomenon has been observed in renal cell carcinomas, neuroblastomas, malignant melanomas and germ cell tumors of the testes. Most vanishing tumors in the CNS are eventually diagnosed as PCNSLs or as a demyelinating disease such as multiple sclerosis [3]. Usually these cases present with neurological symptomatology and often inconclusive biopsies, at least at presentation, with a definitive diagnosis made at the time of recurrence [5]. Here we describe an unusual case of an elderly patient who was diagnosed but not treated for PCNSL, and went into a spontaneously durable remission.

Figure 1. Brain MRI.

Figure 2. Tumor biopsy.

Case report

In January 2014, a 69-year-old female presented to the emergency room after developing severe right flank pain and hematuria. Past medical history was significant for coronary artery dissection, hypertension, hyperlipidemia, hypothyroidism and kidney stones. A renal ultrasound revealed a 0.7 cm stone in the mid right ureter with moderate right hydronephrosis. Following administration of pain medication the patient sustained an episode of hyporesponsiveness, which was reversed by naloxone. Due to her hyporesponsive episode, a head CT scan was performed which showed focal vasogenic edema in the right inferior frontal lobe raising the concern for an underlying mass. MRI of the brain showed a bilobed enhancing lesion in the medial right frontal lobe with surrounding edema (Figure 1). At presentation, she had no focal neurologic symptoms. She denied any numbness, headaches, weakness, coordination or cognitive difficulties. Her admission blood work was unremarkable and HIV testing was negative. The patient denied fevers, weight loss or night sweats. A stereotactic brain biopsy was performed which showed a CD20 positive diffuse large B-cell lymphoma with focal necrosis (Figure 2A). The tumor cells were positive for Epstein-Barr virus (EBV) by *in situ* hybridization (Figure 2B). The tumor cells were negative for CD10 and the biopsy material contained diffuse infiltrates of CD3-positive T cells, CD68 positive histiocytes and microglia, and GFAP positive reactive astrocytes. Immunoglobulin heavy chain rearrangement studies by PCR showed a monoclonal immunoglobulin heavy chain gene rearrangement with a 95 bp peak, confirming a clonal population of B cells.

A computed tomography chest/abdomen/pelvis was performed subsequently, which showed no masses or lymphadenopathy. Eye examination was unremarkable with no evidence of vitritis.

The lesion on the initial MRI at presentation was $14 \times 11 \times 16$ mm (Figure 1A). The patient presented for follow-up at our hospital a month after her diagnosis and was asymptomatic without treatment and off steroids (she was only on a few days of perioperative steroids), so we performed another MRI. This time the imaging revealed an interval decrease in size of the mass, measuring $4 \times 6 \times 9$ mm. As the patient remained asymptomatic and the tumor was shrinking, she remained under active observation with no treatment.

The next MRI, 2 months after diagnosis showed further decrease of contrast enhancement and further MRIs showed complete remission of the tumor at about 4 months after diagnosis (Figure 1B). All follow-up MRIs were on a 3-month interval basis, for a total of 2.5 years. They all remained clear of abnormal enhancement.

Discussion

Current management concepts for PCNSL are continuously being assessed by prospective clinical trials [4]. However, at this time given the rarity of this cancer and the lack of large-scale clinical trials, there is no agreed upon standard of care. Historically, PCNSL was treated with whole-brain radiotherapy (WBRT). An early trial, RTOG 8315 studied WBRT in newly diagnosed PCNSL. It noted a 39% complete response (CR) rate with an overall survival (OS) of 11.6 months and a 2 year progression-free survival (PFS) of 25%. While effective, WBRT alone does not provide durable remissions [5]. The most effective treatment for PCNSL consists of high-dose methotrexate based chemotherapy. NABTT 96-07 was a multicenter trial reported in 2003, studying high-dose methotrexate chemotherapy with deferred radiotherapy. It achieved a CR rate of 52% with OS not reached at 22.8 months [6]. At the time, it established methotrexate as the standard of care chemotherapy agent. In the ensuing years, newer methotrexate based regimens have been introduced. Given the neurocognitive concerns regarding WBRT, dose-intensive chemotherapeutic strategies as consolidation in PCNSL have been developed to replace WBRT consolidation. In the study of Rubenstein *et al.* [7] patients received remission induction therapy with methotrexate, temozolomide, rituximab and, as part of a two-step approach, high-dose consolidation with etoposide plus cytarabine. The study showed the regimen achieved a CR rate of 66% with a PFS of 2.4 years and OS not reached with follow-up of 4.9 years. The results demonstrate that dose-intensive consolidation in PCNSL is feasible and yields rates of PFS and OS at least comparable to those regimens involving WBRT.

Given the limited durability of responses observed in many studies of PCNSL, there is increasing interest in high-dose chemotherapy followed by autologous stem cell transplantation as first line consolidative therapy for PCNSL, thus providing an alternative to address chemoresistance and overcome the blood–brain barrier. Omuro *et al.* describe a Phase II trial where patients received 5–7 cycles of rituximab, methotrexate, procarbazine and vincristine [8]. Those with complete or partial response proceeded with consolidation high-dose chemotherapy with thiotepa, cyclophosphamide and busulfan, followed by autologous stem-cell transplant and no radiotherapy. This treatment was associated with excellent disease control and OS (2-year PFS of 79%), and acceptable toxicity profile and no evidence of neurotoxicity. While the standard of care for PCNSL has yet to be defined, rapid improvements in outcomes have occurred in recent years. Incorporation of newer targeted agents and immunotherapy will likely lead to further advances in outcome.

While the outcome of patients with PCNSL is improving, our case of spontaneous remission suggests that not all patients are in need of active therapies. Spontaneous regression of low-grade lymphoma reportedly occurs in about 10% of the cases [9,10] whereas spontaneous regression of aggressive lymphoma after biopsy has rarely been observed in immunocompetent patients. However, in the context of immune compromise, such as HIV patients, patients on immunosuppression for autoimmune diseases or post-transplantation, amending aspects of the immune response can lead to spontaneous regression of lymphoma. For example, diffuse large B-cell lymphoma accounts for the large majority of AIDS related non-Hodgkin lymphoma and cases have been reported where antiretroviral therapy can lead to immune reconstitution of HIV-infected patients causing regression of the lymphoma [11]. There are also numerous reports of lymphoproliferative disorders, often EBV positive, diagnosed during immunosuppressive treatment for underlying autoimmune disease or organ transplantation that spontaneously resolve after discontinuation or reduction in the immunosuppression [12,13].

The elderly population constitutes a part of the population that tends to have characteristics of immune compromise. The literature has elucidated fluctuations in the efficiency of the immune response, collectively termed immunosenescence. With increasing age, the hematopoietic stem cells differentiate preferentially into myeloid progenitors at the expense of the lymphoid lineage [14]. Antigen-presenting function of monocytes/macrophages is impaired, thus hampering CD4+ T-cell activation [15]. Due to thymic involution, the hallmark of immunosenescence, the output of newly generated naive T cells is dramatically decreased [16]. Additionally, IL-6 increases suppressive myeloid cells and their ability to inhibit antitumor T-cell responses [17]. Thus, senescence establishes immunosuppression facilitated tumor outgrowth by increasing myeloid derived suppressor cells capable of inhibiting T-cell function. Spontaneous regression of diffuse large B-cell lymphoma has been reported in the elderly and may be a direct effect of the immune system waxing and waning. In our patient, she had no underlying immune deficiencies and was not on any immunosuppressive medications. Given her lymphoma was EBV positive, similar to those seen in immunosuppressed organ transplant patients, it is possible the waxing and waning of her immune system may have allowed her lymphoma to arise and then remit.

Given how rarely spontaneous regression of lymphoma is reported, why do we not identify such vanishing tumors more often, especially in the elderly? One possibility is that a transient asymptomatic lymphoma may never come to medical attention. Our case was diagnosed incidentally. Cases may occur then resolve with no clinical symptoms and hence are never diagnosed. Others may present as innocuous symptoms such as headaches that then resolve, missing the diagnosis. Finally, it is likely that some patients receive multi-agent chemotherapy or radiation therapy soon after diagnosis. Given the risk of neurologic injury from a growing tumor, all patients are immediately treated, including those that might have spontaneously resolved. In this patient, by being patient and holding on active treatment, the lymphoma was allowed to spontaneously regress over 4 months. The management issue is identifying patients who might have a spontaneous remission. In our case, the tumor was EBV-positive similar to that seen in immunocompromised hosts such as post-transplant lymphoproliferative disorder where remissions without chemotherapy or radiation therapy may occur. In addition, the tumor biopsy showed T cells and histiocytes suggestive of an inflammatory setting. These features might help identify potential candidate for observation. The hope would be that in the future, identifying patients similar to ours may allow some patients to avoid active therapy for their CNS lymphoma.

Our report has weaknesses related to any case report. With only a single uncontrolled case, one cannot fully assess the frequency by which this situation occurs. In addition, she received steroids immediately after her brain biopsy which may have been directly therapeutic for her lymphoma. In general, patients with CNS lymphomas who enter a CR with steroids alone have dramatic responses while on steroids and then relapse weeks to months after the steroids are discontinued. In our patient, the duration of steroids was less than a week during her immediate hospitalization and on follow-up a month later, she still had a measurable tumor with only minimal change from her presteroid measurement. The tumor then resolved slowly over the following 4 months after her biopsy with no further steroids and remained in remission over 2.5 years later. While one cannot rule out that her response was due to her short steroid use, her case is not typical.

This report demonstrates that PCNSL can follow a self-limited clinical course without antineoplastic therapy. In view of data generated in the elderly population attributing immune deficiencies to senescence, this report is highlighting the etiology and possibly the management of PCNSL in a subset of elderly immunocompetent patients. Care should be taken when deciding on treatment in these patient groups. We are by no means suggesting that we should delay treating as patients might be put in harms way, but more so be skeptical and more observant in cases of potentially immunocompromised patients belonging in the above groups as spontaneous remissions though rare are possible. In the future methods of boosting the immune system such as CART cells and PD1 antibodies may allow more people to avoid cytotoxic chemotherapy.

Conclusion & future perspective

The age of immunotherapy in oncology has arrived. Dramatic changes are occurring in all areas of oncology as a result. In the past, CNS lymphomas could be cured in immunocompromised patients such as PTLN by reversing immunosuppression. However, immune manipulation was not available to patients with an intact immune system. Our case report suggests that some patients with 'intact' immune systems may be immunoresponsive. Going forward with newer therapies, such as CART cells and PD1 antibodies, being developed to augment a normal immune system, immunotherapy will likely play a larger role.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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