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Primary CNS T-Cell Lymphoma: A Case Report on a Solitary Cerebellar Lesion and Review of Current Relevant Literature

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ABSTRACT

Primary central nervous system lymphoma of T-cell lineage (PCNSTL) is an extremely rare entity, with relatively few cases reported in the literature. Presented here is a case of a 44-year-old, HIV negative woman found to have a solitary cerebellar lesion following presentation to the Emergency Department with a fall. The lesion responded to emergent dexamethasone and was followed with serial MRI imaging, which continued to show lesion regression. The lesion was shown to have recurred on MRI 14 months post-presentation and found to be T-cell lymphoma following immunophenotyping and TCR gene rearrangement studies of tissue specimen obtained via excisional biopsy.

Keywords: Primary CNS; Lymphoma; Methotrexate; T-Cell

1. Introduction

Primary CNS lymphoma (PCNSL) is a rare form of extra-nodal NHL with an incidence estimated to be in the vicinity of 1:100,000, making up approximate 4% of primary brain tumours [1,2]. The vast majority of PCNSL are of B-cell lineage (PCNSBL). In the western world T-cell lymphoma is estimated to make up 1% - 3.6% of PCNSL, making it an extremely rare primary brain tumour [3,4].

The presentation of PCNSTL is most often related to the anatomical location of the lesion or to mass effect. Presentation with so-called "B" symptoms is less common [3].

Following the compilation of the largest ever series of PCNSTL, the International Primary CNS Lymphoma Collaborative Group (IPCG) suggest methotrexate (MTX) based on chemotherapeutic regimens should be considered for all PCNSTL patients [3]. Indeed, they found MTX treatment to be associated with better outcomes and it is considered a prognostic indicator.

The IPCG case series found the median overall survival and disease-specific survival for all patients was 25 months (95% CI 11 - 38 months) [3]. The 2- and 5-year DSS were 51% (95% CI 35% - 66%) and 17% (95% CI 6% - 34%) respectively [3].

Presented here is a case of a solitary cerebellar mass confirmed by immunophenotyping and T-cell receptor gene rearrangement studies to be a T-cell lymphoma.

2. Case Report

A 44-year-old, HIV negative female presented to the emergency department following a fall. She had been previously well and has no significant medical history. On examination she had a broad-based, unsteady gait. No other cerebellar signs were present. The remainder of the neurological and general medical examination was unremarkable. As part of the work-up for fall and unsteady gait the patient underwent a CT scan of her head with contrast. This showed a round intra-parenchymal contrast enhancing left cerebellar lesion measuring 30 × 24 × 21 mm with surrounding low attenuation. Midline shift and significant mass effect were present in the posterior fossa. CT angiography was normal. Dexamethasone 4 mg QID was started with subsequent rapid improvement of gait abnormalities.

MRI scanning the following day showed an intra-axial lesion of 22 × 19 × 18 mm. Further MRI imaging two weeks later showed continued regression of the lesion (15 × 9 × 10 mm) and the patient remained asymptomatic

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and free of clinical signs. The main differentials at this stage were: tumefactive MS process, monophasic demyelinating lesion, resolving haematoma and lymphoma. Serial MRI imaging was planned for future follow-up.

MR scanning at 3- and 8-month following presentation continued to show resolution of the cerebellar lesion and the patient remained asymptomatic and untreated. At 14 months post initial presentation MRI showed an enhancing lesion 40 × 28 mm in the left cerebellar hemisphere. The patient remained asymptomatic. The working diagnosis at this stage was Lhermitte-Duclos disease.

Excisional biopsy was performed approximately three weeks later. Pathology was suggestive of a malignant lymphoma with florid atypical lymphoid infiltrate. Immunohistochemistry was most in keeping with a T-cell lymphoma, with positive CD3, CD5 and bcl2.

Postoperative PET scan was negative. Post-operative MRI showed minimal residual tumour. The patient recovered well following surgery with minimal gait disturbance that was resolved with rehabilitation. Treatment was instituted by oncology with intravenous (IV) and intrathecal (IT) methotrexate. Serial MRI showed a stable appearance with a small residual nodular focus of 2 mm and scant contrast uptake.

The patients remain asymptomatic and free of neurological signs.

3. Literature Review

An extensive search of the current relevant literature was conducted via PubMed. Literature relating to PCNSL, PCNSTL, and specifically PCNSTL originating in the cerebellum was reviewed. All relevant referenced articles and authors were also reviewed where possible.

The literature relating specifically to PCNSTL is quite sparse and at times seemingly contradictory. Due to the extreme rarity of PCNSTL it has been difficult in the past to make any generalizations or define a common pattern for the disease. While the literature suggests it should remain difficult to identify a "typical" PCNSTL picture, there are some recurred suggestions, particularly regarding optimal diagnosis, prognosis and treatment.

4. Incidence

The current estimated incidence of PCNSL and PCNSTL varies throughout the literature. In the beginning of the 1990's the National Cancer Institute Surveillance, Epidemiology and End Results Program calculated the incidence of PCNSL as 1:1,000,001. Most authors suggest this make up 3% - 6% of all primary brain tumours [4].

The true incidence of PCNSTL is largely unknown. Incidence suggested by most authors is in the vicinity of 1% - 3.6% of cases of PCNSL based on large series' of PCNSL [3]. The largest of its kind in the western world presented by Ferreri *et al.* consisted of 378 cases of diagnosed PCNSL, of which 8 (2%) was PCNSTL [5-7]. There are reports suggesting the incidence of PSCNTL is much higher in eastern countries. In a nationwide survey of histologically proven PCNSL conducted in Japan, Hayabuchi *et al.* found PCNSTL to have an incidence of 8.5% [8]. It is currently unknown whether this is due to a genuine ethnic variation or due to the difficulties in establishing a reliable histological diagnosis.

The incidence of PCNSL of any histological type is much higher in immunocompromised groups, such as patients with AIDS or immune-suppressed transplant patients. The incidence of PCNSL neoplasm in the AIDS population (4.7 per 1000 person years) is approximately 3600 times than that in the general public [9,10].

5. Presentation

Primary CNS T-cell lymphoma often present with signs of increased intracranial pressure or focal neurological deficit related to the site of the space occupying lesion, much the same as a B-cell lymphoma [11]. It is often proposed however, that PCNSTL differs from PCNSBL in terms of age of presentation, gender, location of the lesion and patient survival [12]. Based on the scarcity of published data it is difficult to either support or refute the aforementioned theory completely. The International PCNSL collaborative Group (IPCG) in their case series of PCNSTL patients found there to be no significant difference in patient age when compared with the International Extranodal Lymphoma Study Groups (IELSG) compilation of 378 PCNSL patients, 98% of whom had been diagnosed with PCNSBL. The IPCG showed a median age of 59.5 years with a range of 3 - 84, while the IELSG showed a median age of 61 years and a range of 14 - 85 [3,5-7]. If anything can be taken from this, it could be that an individual affected with PCNSL at the younger extreme of age is more likely to suffer from a tumor of T-cell lineage.

Primary central nervous system lymphoma of T-cell lineage has a male predominance, as does PCNSBL. The IPCG data shows a male:female ratio of 3.5:1 which is significantly higher than the approximate 1.4:1 ratio found in the IELSG data of mostly B-cell lineage tumors. The male predominance appears to be a steadfast phenomenon, however not always to the extent found in the IPCG data. The male to female ratio's in the literature for PCNSTL is in the order of 1.7 - 2.2:1 and for PCNSBL 1.4 - 2.0:1 [6,7,12-14]. There does appear to be a trend to a slightly greater male predominance in T-cell variant compared with B-cell variant, however the significance of this in light of the much greater numbers of PCNSBL compared with PCNSTL is unknown to the current authors.

A predilection for T-cell lymphoma to effect the in-

fratentorial structures has been reported [12]. The rates of infratentorial involvement with PCNSTL is also said to be higher than that of PCNSBL. In a review of 24 PCNSTL cases Villegas *et al.* found the posterior fossa involved in 54% of cases compared with 12% - 29% in series of mostly B-cell PCNSL [12]. Takeshita *et al.* approximated the posterior fossa was involved in 44.8% of PCNSTL cases [11]. The data from the IPCG shows the posterior fossa was involved in 16% of patients. The IELSG data (of mostly B-cell tumors) shows the posterior fossa contents are affected in 12% of cases. As with much of the literature on PCNSTL it is difficult to compare the numbers with those of their B-cell counterparts due to the asymmetry in numbers of cases reported. It cannot be categorical stated that PCNSTL has a predilection for the posterior fossa. It could be inferred however that T-cell lymphomas are at least slightly more prone to the posterior fossa than B-cell lymphomas based on current data.

6. Diagnosis

Findings on imaging studies consistent with diagnosis of PCNSL in an immunocompetent patient include: a relatively homogenous lesion; isointense with grey matter on MRI and hyperdense on CT; and dense contrast enhancement [15]. These findings obviously are not specific enough to effectively diagnose PCNSL, least of all PCNSTL. A high grade glioma may share much of the mentioned characteristics [15]. Because of the rarity of PCNSTL no typical clinical, radiological or pathological pattern emerges, causing some difficulty with diagnosis.

The approach to the pathological diagnosis consists of immunohistochemistry and often gene rearrangement studies. One of the major difficulties encountered is differentiating neoplastic T-cell processes from reactive, inflammatory T-cell processes [4,16]. Immunohistochemical analysis is performed to identify alterations in T-cell surface marker expression which may suggest neoplastic transformation [4,16]. Some common antigens analysed include CD3, CD5, CD7 and CD204. The Ki67 index, a cellular marker of the degree of proliferation, is often assayed. It is sometimes quite variable and of questionable utility [4].

Immunohistochemical analysis is often bolstered by molecular gene studies to improve accuracy of diagnosis. Clonality studies of T-cell receptor gamma gene rearrangements are often most influential in the diagnosis of PCNSTL [4]. There is often a high degree of similarity between T-cell lymphoma and reactive infiltrates with respect to cytomorphologic and immunophenotypic features, requiring TCR gene rearrangement studies to differentiate between the two [4].

Dulai *et al.* in their paper on the diagnosis of CNS T-cell lymphoma offer a comprehensive discussion of the immunohistochemical and molecular diagnosis of PCNSTL and readers are referred there.

7. Treatment

The approach to treatment of lymphomas of the CNS, of any cell lineage, involves the utilisation of chemotherapy and/or radiotherapy. Much debate surrounds the most appropriate treatment regime. The debate focuses on which modalities are proven to achieve greatest response rates and in which combination; usefulness of adjuncts to IV chemotherapy such as blood-brain barrier disruption (BBBD) and autologous peripheral-blood stem-cell transplantation (APBSCT); and most effective methods of acquiring adequate cure rates whilst minimising neurotoxicity [6].

There have been no randomised controlled trials conducted to assess efficacy of various treatment approaches to PCNSL and so current therapeutic knowledge is based on non-randomised trials, meta-analyses of patient series and retrospective studies. Whilst this is obviously far from ideal, there is a general consensus among published data that combined chemo-radiotherapy is superior to radiotherapy alone and that chemotherapy regimens that include high dose IV methotrexate (MTX) achieve better results than those without high dose MTX [3,5-7].

In a large multicentre study of treatment of PCNSL involving 370 patients (mostly with a B-cell lineage tumour), Ferreri *et al.* found that the treatment modality used is correlated with patient outcome [5]. Two year overall survival was 25% ± 4% for patients treated with radiotherapy alone, 35% ± 8% for radiotherapy followed by chemotherapy, 34% ± 10% for chemotherapy alone and 45% ± 3% for chemotherapy followed by radiotherapy [5]. The difference in survival between the radiotherapy group and the three others was significant, however the difference between these "other" groups was not significant [5].

Ferreri *et al.*, in the same study concluded high dose MTX is the most effective chemotherapeutic agent with an 80% - 90% response rate and a 2-year overall survival rate of 60% - 65% [5].

In the Summary Statement on PCNSL, high dose MTX used as a single agent had a response rate of 52% - 88% and 70% - 94% when combined with other agents [6]. Use of high dose MTX is considered a prognostic indicator and patients without high dose MTX indeed appear to do less well [3,5-7]. Any chemotherapeutic regime without high dose MTX can be considered to have comparable results to a radiotherapy only treatment regime [5].

The use of whole brain radiation therapy (WBRT) in combination with chemotherapy provides survival benefits over using radiotherapy alone, however its use is associated with significant neurotoxicity [6]. Combined

chemo-radiotherapy is associated with severe neurologic impairment in 40% of patients and neurotoxicity-related mortality of 30% [6]. In a study on therapy for PCNSL, Deangelis *et al.* found high dose MTX, followed by WBRT and post-radiation cytarabine, causes neurotoxic complications as frequently in the under 60 age group as it did in the over 60 age group [17]. Ferreri *et al.* found the addition of intrathecal chemotherapy increased the risk of neurotoxicity. To add to this, intrathecal chemotherapy did not improve survival beyond that of IV high dose MTX chemotherapy [5,6].

Based on the increased risk of neurotoxicity when WBRT is combined with chemotherapy some authors suggest the best role for radiotherapy may be as salvage treatment combined with chemotherapy in refractory or recurrent disease. Randomised controlled trials are required to justify such statements and also to interrogate the usefulness of BBBD and APBSCT in treatment of PCNSL.

8. Prognosis

Many authors have described and attempted to verify prognostic indicators that can be used to stratify patients into risk groups to facilitate appropriate management. In their publication, Prognostic Scoring System for Primary CNS Lymphoma, The International Extranodal Lymphoma Study Group proposed a prognostic scoring system based on; patient age, performance status, serum lactate dehydrogenase level, CSF protein concentration and involvement of deep brain structures (periventricular regions, basal ganglia, brainstem, and/or cerebellum) [7]. The study found patient age > 60 years, performance status scored as more than 1 (based on the Eastern Cooperative Oncology Group [ECOG] performance status scale), elevated serum LDH level, high CSF protein concentration, and involvement of deep brain structures were significantly and independently associated with a worse survival. The authors of the aforementioned study commented on the need for the scoring system and its relevance in therapeutic decision making to be assessed in further studies.

The fact that a vast proportion of the literature on PCNSL, and particularly PCNSTL, is based on retrospective studies makes it difficult to validate such prognostic scoring systems. For instance, in the case series of PCNSTL compiled by the IPCG, which is the largest of its kind originating from the western world, complete information on all five prognostic factors was available for only 14 of the 45 patients. The authors of the IPCG case series elude to their study having insufficient power to demonstrate any significant relationship between both age and lesion site and patient prognosis. In this series however, ECOG performance status ≤ 1 and use of high dose MTX were found to influence survival. This is a fact often corroborated.

The literature is at times equivocal on the topic of prognosis and patient survival. Particularly with respect to the matter of prognosis of PCNSTL vs PCNSBL. Fundamentally, the prognosis of PCNSL of any cell lineage is poor, although it has improved with the continued evaluation and advancement of current diagnostic, prognostic and treatment approaches. With so few numbers of PCNSTL reported it is difficult to gauge an accurate estimate of prognosis. The IPCG case series found the median overall survival and disease-specific survival for all patients was 25 months (95% CI 11 - 38 months) [3]. The 2- and 5-year disease specific survival were 51% (95% CI 35% - 66%) and 17% (95% CI 6% - 34%) respectively [3]. Some studies have suggested a diagnosis of PCNSTL carries a worse prognosis than PCNSBL. Others still have suggested PCNSTL more often displays low-grade features and would thus carry a better prognosis. The authors of the IPCG case series concluded the outcomes for patients with either PCNSTL or PCNSBL were generally similar.

9. Discussion

Primary central nervous system lymphoma of T cell lineage is an extremely rare entity. With relatively few cases reported in the literature compared to its B-cell counterpart, many of the epidemiological and clinical features of PCNSTL remain enigmatic. The reported incidence varies somewhat from the western world to the east, with an incidence estimated at 1% - 3.6% of all PCNSL in the western world, to 8.5% of all PCNSL in Japan [3,4,8]. Considering the accepted incidence of PCNSL is 1:100,000, whichever incidence value is used, it is obvious that PCNSTL is extremely rare [1,2].

We presented here a case of a 44-year-old HIV negative, immunocompetent female who presented to our emergency department following a fall and was subsequently found to have a round intra-parenchymal contrast enhancing left cerebellar lesion which responded to emergent dexamethasone. Following the course of treatment and investigation outlined in the case report above, our patient was diagnosed with PCNSTL subsequent to pathological examination of the excisional biopsy specimen.

As mentioned throughout the literature review, the paucity of published data on PCNSTL makes it difficult to outline a typical PCNSTL clinical scenario, however our patient shared many characteristics with the trends found in the literature.

Our patient presented with a fall following development of an unsteady gait on a recent background of no symptoms whatsoever. Obviously this could easily and appropriately be explained by the site of the lesion, and associated oedema within the cerebellum and is consis-

tent with PCNSTL often presenting secondary to effects caused by the site of the lesion within the brain.

In terms of treatment, this was largely consistent with examples found in the literature, both with respect to the emergent dexamethasone in the emergency department and the IV/IT MTX. Corticosteroids alone may produce a rapid and substantial tumor regression in up to 40% of PCNSL patients [6]. This effect was apparent in our patient as demonstrated by radiographic evidence of tumour regression and by resolution of symptomatology. Consistent with the growing body of evidence regarding optimal treatment of these malignancies, IV MTX was used as primary treatment in this case, along with supplementary IT MTX. Indications for and efficacy of intrathecal MTX are unclear. Ferreri *et al.* found in there case series that the addition of IT MTX was associated with a higher incidence of neurotoxicity and did not improve survival in patients treated with primary chemotherapy containing high dose MTX [5]. This could be considered in the future treatment of similar cases at our centre. Although, the likelihood of encountering another PCNSTL case in the foreseeable future is low and it is possible that further advancements will be made in the understanding and approach to treatment of PCNSTL in the interim.

The difficulties faced in terms of developing best practice guidelines for PCNSTL are obvious. With such a rare disease and so few reports in the literature it is difficult to produce powerful, methodologically sound studies. We present this case of PCNSTL to add further to the scarce literature on this extremely rare primary brain tumour.

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