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Case Report Open Access

Recurrent Primary CNS Lymphoma Presenting with Central Neurogenic Hyperventilation

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Abstract

Background: Tumor-induced Central Neurogenic Hyperventilation (CNH) is exceedingly rare, about half resulting from Primary CNS Lymphoma (PCNSL) despite their rarity.

Results: We present a 75 year-old, immunocompetent woman with recurrent PCNSL leading to CNH. She was initially diagnosed with PCNSL via biopsy of the single enhancing left caudate focus among diffuse, nonenhancing CNS infiltrative disease without diffusion restriction or CSF or intraocular dissemination. She received 5 cycles of biweekly rituximab and methotrexate, initially dosed at 3.5 gm/m^2 with procarbazine and vincristine, then dosed at 8 gm/m^2 with monthly temozolomide 150 mg/m^2. Repeat brain MRI revealed no residual enhancement with confluent subcortical nonenhancing signal without brainstem involvement suggesting methotrexate-related leukodystrophy. Two weeks after cytarabine consolidation, she presented with intractable emesis without gastrointestinal cause. A week later, she developed marked tachypnea without cardiopulmonary etiology. Blood glasses revealed respiratory alkalosis (maximal pH=7.67, respiration=27, pO_2=241; minimum pCO_2=10). She remained otherwise neurologically intact. For suspicion of CNH, she was intubated and brain MRI revealed progressive nonenhancing disease without restricted diffusion extending periventricularly from dorsal midbrain to vermis. CSF profile revealed normal protein (40 mg/dL), RBC 97/μL, WBC 3/μL (88% lymphocytes) with negative bacterial cultures, toxoplasma IgG and HSV, JC, CMV, EBV and JC PCRs. Flow cytometry and cytology revealed no lymphoma cells. Brain and body PET revealed avid FDG-uptake in the new periaqueductal nonenhancing tumor, confirming lymphoma recurrence; no extracranial disease was evident. Her CNH resolved though remission was only brief following posterior fossa radiation (30Gy, 17fx), dexamethasone 40 mg/day, and off-label nivolumab 3 mg/kg q 2 weeks. Repeat brain MRI revealed diffuse cerebral nonenhancing disease progression at 4 months after recurrence. She died shortly after transfer to hospice.

Conclusion: This represents the first recurrent PCNSL leading to CNH, which was a presenting symptom in all prior PCNSL cases reported and lead to death in the majority.

Keywords: CNS lymphoma; Central neurogenic hyperventilation; Radiation

Introduction

Tumor-induced central neurogenic hyperventilation (CNH) is exceedingly rare. CNH is defined by hyperventilation with low arterial $PaCO_2$, high arterial PaO_2, and high arterial pH without drug or metabolic causes [1,2]. Most cases of tumor-induced CNH result from primary CNS despite their rarity, comprising only 4% of primary CNS tumors [2,3]. Tumor-induced CNH resulted from CNS lymphoma in nearly 60% of tumor-induced CNH [2,4-15]. Most tumor-induced CNH results from infiltrating tumor in the pons or medulla, less commonly in the setting of diffuse cerebral disease [2,5]. The presumed mechanism is activation of respiratory centres and central chemoreceptors [2]. All previously reported cases presented with CNH at diagnosis. We present an immunocompetent woman with previously diagnosed PCNSL presenting with CNH at first recurrence. Tumor-induced CNH proved uniformly fatal in essentially all cases.

Case Presentation

A 75 year-old, immunocompetent woman presented with months of progressive dementia and aphasia. A brain MRI revealed diffuse cerebral, predominantly subcortical, non-enhancing disease (Figure 1A). There was a single site of enhancement in the left caudate and negligible diffusion restriction noted (Figures 1B-1C). Stereotactic biopsy of single enhancing lesion revealed pathology consistent with diffuse large B cell lymphoma. Hematoxylin and Eosin (H&E) showed large atypical lymphoid cells in an angiocentric pattern and with scant cytoplasm, large pleomorphic nuclei with clumped chromatin, nuclear moulding and occasionally prominent nucleoli (Figure 2A). Scattered mitoses were seen. Immunohistochemistry was positive for CD20 (Figure 2B) and MUM1. Subsets were positive for BCL2 and BCL6 and few for CD10. Small mature CD3 T lymphocytes infiltrate was detected. The Ki67 proliferation index was as high as 80-90% (Figure 2C).

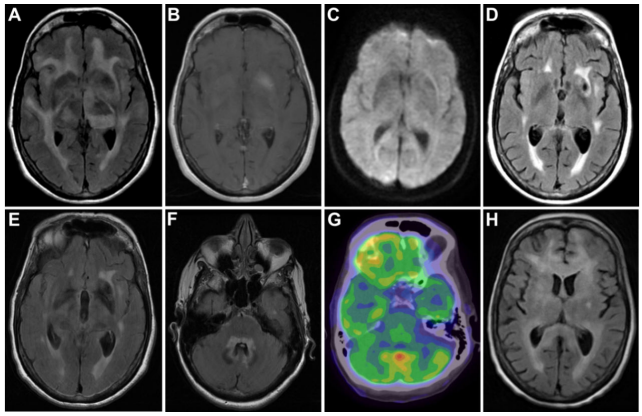

Figure 1: Brain imaging findings. Brain MRI findings were atypical for primary CNS lymphoma (PCNSL), defined by predominantly non enhancing disease on fluid attenuation inversion recovery (FLAIR) images (A,D,E,F,H) and no associated restricted diffusion was ever noted (C). FLAIR diseases was restricted to cerebral hemispheres at presentation (A), limited to periaqueductal grey brainstem at recurrence (E-F) and diffuse but predominantly supratentorial prior to death (H). The single faintly enhancing focus in left caudate (B) at presentation was targeted for biopsy. Remission was notable for residual FLAIR signal restricted to subcortical white matter and consistent with methotrexate-induced leukodystrophy (D). The recurrent disease in the brainstem presenting with central neurogenic hyperventilation was avid on fluorodeoxyglucose positron emission tomography (FDG-PET, G).

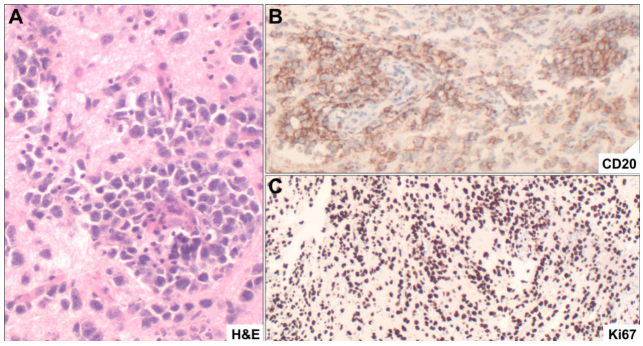

Figure 2: Pathology of brain biopsy. H&E shows large atypical lymphoid cells in an angiocentric pattern and with scant cytoplasm, large pleomorphic nuclei with clumped chromatin, nuclear molding, and occasionally prominent nucleoli (A, 4x). Scattered mitoses seen. Immunostaining: positive for CD20 (B, 4x), MUM1; subset positive for BCL2, BCL6; few positive for CD10. Small mature CD3 T lymphocytes infiltrate lesion. Ki67 index up to 80-90% (C, 4x).

Brain and body Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) revealed no systemic involvement, consistent with Primary CNS Lymphoma (PCNSL). Flow cytometry and cytology revealed no Cerebrospinal Fluid (CSF) dissemination. A bone marrow biopsy revealed mild B-cell lymphocytosis inconclusive for marrow involvement. She was treated with 5 cycles of biweekly intravenous rituximab (500 mg/m^2) and methotrexate. Methotrexate was increased from 3.5 to 8.0 gm/m^2 while the initial procarbazine (100 mg/m^2) and vincristine 2 mg was switched to monthly temozolomide (150 mg/m^2) for a total of 2.5 months of therapy. After repeat brain MRI revealed remission (Figure 1D), she underwent consolidation therapy with cytarabine (3 gm/m^2 day 1-2, q3 weeks). Over the course of this therapy, she improved clinically with a dramatic improvement in her initial encephalopathy, once again living independently.

At 4 months from diagnosis and shortly after consolidation therapy, she developed intractable emesis without clear gastrointestinal cause and hyperventilation without cardiopulmonary etiology. Serial blood glasses marked revealed respiratory alkalosis (maximal pH=7.67, respiration=27, pO_2=241; minimum pCO_2=10). She remained otherwise neurologically intact. For suspicion of central neurogenic hyperventilation (CNH), she was intubated and brain MRI performed. While there was no clear supratentorial disease progression (Figure 1E), there was new non enhancing FLAIR disease extending from dorsal midbrain to the vermis (Figure 1F). Repeat brain FDG-PET revealed high glucose uptake associated with the new FLAIR disease in the pontine tegmentum (Figure 1G), consistent with recurrent PCNSL. CSF profile revealed normal protein (40 mg/dL), RBC 97/μL, WBC 3/μL (88% lymphocytes) with negative bacterial cultures, toxoplasma IgG and HSV, JC, CMV, EBV and JC PCRs. Flow cytometry and cytology again revealed no lymphoma cells.

To palliate and spare cognitive neurotoxicity, she was treated with involved field radiation to posterior fossa radiation (30Gy in 17 fractions), dexamethasone 40 mg/day, and off-label nivolumab 3 mg/kg q2 weeks with resolution of CNH. Disease remission was only brief. By 4 months after recurrent PCNSL presenting with CNH, brain MRI revealed diffuse non enhancing disease progression, including the brainstem but more pronounced in the cerebral hemispheres (Figure 1H). She was transferred to hospice and died shortly after 9 months after her initial diagnosis.

Discussion

Central Neurogenic Hyperventilation (CNH) is exceedingly rare and portends poor prognosis in reported cases. Despite their rarity, comprising only 1% of all CNS tumors, CNS Lymphoma (CNSL) leads to 58% (15/26) of reported cases, mostly (13/15) Primary CNS Lymphoma (PCNSL) [2,4-15]. The remaining cases were comprised of 31% (8/26) gliomas [16-23], <4% (1/26) medulloblastoma [24], <4% (1/26) ganglioglioma [25] and <4% (1/26) invasive laryngeal carcinoma [26]. 77% (20/26) of tumor-induced CNH cases resulted from direct tumor infiltration into the pontine tegmentum and medulla, leading to activation of respiratory centres and central chemoreceptors [2]. The remaining cases had diffuse cerebral disease, mostly CNS lymphoma cases [2,5]. We present the first case of PCNSL presenting with CNH at recurrence. All prior cases of tumor-induced CNH presented at the time of diagnosis. CNH should raise suspicion of CNS lymphoma in undiagnosed patients and suggest recurrence in confirmed cases of CNS lymphoma. Antineoplastic therapy is vital for controlling PCNSL-induced CNH. Survival is uniformly dismal after presenting with tumor-induced CNH.

Conclusion

We present the first case of recurrent primary CNS lymphoma leading to Central Neurogenic Hyperventilation (CNH). CNH was a

presenting symptom in all previously reported cases of CNS lymphoma, comprising nearly 60% of reported cases of tumor-induced CNH despite their rarity. Tumor-induced CNH raises the probability of CNS lymphoma in undiagnosed cases and of recurrence in diagnosed cases. Tumor-induced CNH predicts short-interval death in most cases.

Practice Points

- Primary CNS lymphoma comprises ~1% of all CNS tumors and ~2.3% of primary CNS tumors.
- Tumor-induced central neurogenic hyperventilation (CNH) is exceedingly rare and uniformly fatal.
- Tumor-induced CNH is caused by CNS lymphoma in nearly 60% of reported cases.
- CNH should raise suspicion of CNS lymphoma in undiagnosed patients and suggest recurrence in confirmed cases of CNS lymphoma.

References

1. Kramer CL, Wijdicks EF (2014) Central neurogenic hyperventilation. Neurology 83: 376.
2. Tarulli AW, Lim C, Bui JD, Saper CB, Alexander MP (2005) Central neurogenic hyperventilation: a case report and discussion of pathophysiology. Arch Neurol 62: 1632-1634.
3. Cbtrotus (2012) CBTRUS 2004-2008 statistical report: primary brain tumors in the United States.
4. Bateman DE, Gibson GJ, Hudgson P, Tomlinson BE (1985) Central neurogenic hyperventilation in a conscious patient with a primary cerebral lymphoma. Ann Neurol 17: 402-405.
5. Enam SA, Ali R (2011) B-cell lymphoma of the brainstem with central neurogenic hyperventilation. J Pak Med Assoc 61: 925-927.
6. Laigle-Donadey F, Iraqi W, Straus C, Martin-Duverneuil N, Fénelon G, et al. (2005) Primary central nervous system lymphoma presenting with central neurogenic hyperventilation. A case report and review of the literature. Rev Neurol (Paris) 161: 940-948.
7. Nakasu Y, Nakasu S, Matsuda M, Handa J (1988) Central neurogenic hyperventilation with pontine tumor. Case report and a review of the literature. Nihon Geka Hokan 57: 165-171.
8. Pauzner R, Mouallem M, Sadeh M, Tadmor R, Farfel Z (1989) High incidence of primary cerebral lymphoma in tumor-induced central neurogenic hyperventilation. Arch Neurol 46: 510-512.
9. Salvesen R (1989) Pontine tumour with central neurogenic hyperventilation. J Neurol Neurosurg Psychiatry 52: 1441-1442.
10. Schmid C, Diem H, Herrmann K, Voltz R, Ott G, et al. (2005) Unusual sites of malignancies: CASE 2. Central neurogenic hyperventilation as a complication of Richter's syndrome. J Clin Oncol 23: 2096-2098.
11. Shams PN, Waldman A, Plant GT (2002) B Cell lymphoma of the brain stem masquerading as myasthenia. J Neurol Neurosurg Psychiatry 72: 271-273.
12. Shibata Y, Meguro K, Narushima K, Shibuya F, Doi M, et al. (1992) Malignant lymphoma of the central nervous system presenting with central neurogenic hyperventilation. Case report. J Neurosurg 76: 696-700.
13. Sugama S, Suda M, Oda M, Tanabe H (1990) Central neurogenic hyperventilation in an awake patient with a primary cerebral lymphoma. Rinsho Shinkeigaku 30: 994-1000.
14. Sunderrajan EV, Passamonte PM (1984) Lymphomatoid granulomatosis presenting as central neurogenic hyperventilation. Chest 86: 634-636.
15. Sakamoto T, Kokubo M, Sasai K, Chin K, Takahashi JA, et al. (2001) Central neurogenic hyperventilation with primary cerebral lymphoma: a case report. Radiat Med 19: 209-213.
16. Gaviani P, Gonzalez RG, Zhu JJ, Batchelor TT, Henson JW (2005) Central neurogenic hyperventilation and lactate production in brainstem glioma. Neurology 64: 166-167.
17. Ledet D, Delos Santos NM, Khan R, Gajjar A, Broniscer A (2014) Central neurogenic hyperventilation and renal tubular acidosis in children with pontine gliomas. Neurology 82: 1099-1100.
18. Siderowf AD, Balcer LJ, Kenyon LC, Nei M, Raps EC, et al. (1996) Central neurogenic hyperventilation in an awake patient with a pontine glioma. Neurology 46: 1160-1162.
19. Tobias J, Heideman R (1991) Primary central hyperventilation in a child with a brainstem glioma: management with continuous intravenous fentanyl. Pediatrics 88: 818-820.
20. Van Wamelen DJ, Hama-Amin AD, Gilhuis HJ, De Bruijn SF (2011) Central neurogenic hyperventilation due to pontine glioma. Neurol India 59: 782-783.
21. Chuang YM, Guo WY, Ho DM, Wong TT, Hung JH, et al. (2003) Skew ocular deviation: a catastrophic sign on MRI of fetal glioblastoma. Childs Nerv Syst 19: 371-375.
22. Shahar E, Postovsky S, Bennett O (2004) Central neurogenic hyperventilation in a conscious child associated with glioblastoma multiforme. Pediatr Neurol 30: 287-290.
23. Toyooka T, Miyazawa T, Fukui S, Otani N, Nawashiro H, et al. (2005) Central neurogenic hyperventilation in a conscious man with CSF dissemination from a pineal glioblastoma. J Clin Neurosci 12: 834-837.
24. Gottlieb D, Michowitz SD, Steiner I, Wald U (1987) Central neurogenic hyperventilation in a patient with medulloblastoma. Eur Neurol 27: 51-54.
25. Diez García R, Carrillo A, Bartolomé M, Casanova A, Prieto M (1995) Central hypoventilation syndrome associated with ganglioneuroblastoma. Eur J Pediatr Surg 5: 292-294.
26. Dubaybo BA, Afridi I, Hussain M (1991) Central neurogenic hyperventilation in invasive laryngeal carcinoma. Chest 99: 767-769.