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A 60-Year-Old Indian Male With Altered Sensorium and Extensive Lymphoma of the Scalp

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Primary cutaneous non-Hodgkin lymphoma (NHL) is an uncommon entity, representing 10% of all extranodal NHLs.¹ Among all cutaneous sites, the scalp is a rare site of presentation. To date, only nine such cases have been reported in the literature²; most of them, however, were considered as NHL of the cranial vault, rather than primary NHL of the scalp. This report presents a diagnostic dilemma in such a case, and the manifestation from its origin on the choice of final management. We have posed this dilemma to an international multi-disciplinary panel as follows: (1) Did this lymphoma likely start from the scalp or skull vault? (2) How should various treatment modalities (ie, chemotherapy and/or radiation) be sequenced for this patient?

CASE PRESENTATION

A 60-year-old man presented to the Oncology Clinic of the Post Graduate Institute of Medical Education & Research (Chandigarh, India) in October 2011 with a complaint of a “swelling” over the scalp noted gradually over 8 months’ time. Eighteen months prior, the patient had fallen and sustained a closed head injury, and fracture of the right femur, which was managed urgently at an outside hospital with external fixation. Currently, the noted scalp swelling was diffuse, gradually increasing in size, and associated with mild superficial pain. Central ulceration occurred over the swelling within 4 months of its appearance. The patient then reported a 4-month history of moderate intermittent headache (localized centrally, with occasional referral to the occipital area), occasional vomiting. Urinary incontinence developed over 1 month's time; he then reported a history of altered sensorium over 2 weeks, and two focal seizures over 2 days’ time. There were no other systemic symptoms. The patient was admitted to the local hospital for evaluation and workup.

Local examination revealed diffuse swelling of the entire scalp, with ulceration predominantly in the central region. The swelling spanned a 12 × 10 cm area, and involved the underlying skull bone, which was grossly destroyed, with the meninges visible and palpable. On general examination there was no lymph node involvement in the anterior or posterior cervical chains. Musculoskeletal and neurologic exams revealed 4/5 strength in all extremities, with no sensory loss.

Baseline hemogram showed a total white blood cell count of 12,700/μL, hemoglobin 9.4 g/dL, platelets 597,000/μL, with differential showing 82% neutrophils, 10% lymphocytes, and 4% monocytes. Computerized tomography (CT) of the head with contrast showed hypodense lesions in the vertex and bilaterally in the parietal regions of the skull, with gross

edema in the underlying brain parenchyma. There was extensive cranial bone (skull vault) erosion. Bone fragments were interspersed in the soft tissue of the scalp. There was infiltration of the scalp with partial ulceration more on the right side including the occipital area (Figure 1A, B, and C). Magnetic resonance imaging (MRI) of the brain revealed T1 hypointense, T2 isointense, heterogeneously enhancing soft tissue nodules (maximum thickness 3 cm), with predominantly extradural and extracranial components, extending across the circumference of the right side, the vertex, and bilateral high fronto-parietal convexities of the skull. There was destruction of the right high fronto-parietal cranial bone, with evidence of nodular enhancing deposits in an extradural location on the right side of the cranium. In addition, there was leptomeningeal enhancement in the right cerebral convexities, as well as the suggestion of parenchymal invasion in the high parietal region. A mass effect was seen in the form of an 8-mm right shift, subfalcine herniation, and rotation of the brainstem to left (Figure 2A, B, and C). Further workup included a contrast-enhanced CT scan of the chest, abdomen, and pelvis, which was normal. Bone marrow examination was normal with normal cellularity. Lumbar puncture was not attempted.

Initial biopsy from the cranial lesion was reported as only stratified squamous epithelium with no evidence of malignancy. A repeat biopsy from the ulcerated swelling on the scalp revealed a histology suggestive of NHL, diffuse large B-cell type. Immunohistochemistry showed that the lymphoma cells were positive for CD3 and CD20 but negative for CD30.

The patient received five of six planned cycles of systemic chemotherapy with cyclophosphamide, doxorubicin, and vincristine each given on day 1, and oral prednisolone given for 5 days (CHOP), every 3 weeks. The intravenous chemotherapy doses were reduced due to the patient's poor performance status. Cost precluded treatment with rituximab. The patient improved symptomatically with clinical regression in the swollen and ulcerated area of the scalp. CT of the brain after five cycles showed reduction in the scalp swelling, as well as the previous bone destruction, with subsequent reformation of the skull bone. However, a new enhancing soft tissue lesion measuring $3 \times 3 \times 1.5$ cm was detected in the scalp in the right temporal and frontal areas, with underlying cerebral edema and bone erosion (Figure 3A and B). There was no definite mass lesion in the brain parenchyma; however, there was midline shift. The patient had one seizure before the sixth scheduled cycle of chemotherapy, and was given palliative irradiation in an 8-Gy single fraction to the whole brain. There was subsequently an 80% reduction in the right temporo-frontal nodule on clinical exam. He was then monitored under palliative care.

We posed the following additional questions toward the management of this patient: (1) How would you proceed in recommending initial treatment for this patient's malignancy, from a multi-disciplinary standpoint? (2) How would you proceed in the light of progression of disease?

HEMATOLOGIST'S EXPERT OPINION

This case illustrates one of the rare forms of NHL involving the cranial vault and underlying brain parenchyma. A non-contributory systemic workup (including CT scan of the whole body and bone marrow biopsy) suggest that this lymphoma has remained localized to the

cranial vault and brain parenchyma for the last 8 months. This lymphoma would be classified as primary cranial vault lymphoma (PCVL).³ ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT of the whole body, though experimental in this indication, would give more information about the systemic spread of the disease.⁴ FDG-PET/CT is superior to contrast-enhanced CT scan of the whole body in staging high-grade lymphomas as it is a functional image of the body.⁵ Various studies have demonstrated an upstaging of lymphomas with PET/CT as compared with contrast CT scan in approximately 20% of cases, with a change in treatment decision occurring in fewer than 15% of cases.⁶

This patient also had a history of trauma to the head before the development of NHL. The relationship of trauma with the development of NHL is controversial. A few studies in the past have found a relationship between trauma and the development of NHL at the site of trauma⁷; however, in the absence of large series of patients with PCVL, it would be difficult to prove a cause-and-effect relationship.

Another interesting point of discussion in this case is speculation upon the origin of lymphoma.⁸ From the patient's history, it appears that this lymphoma originated from the scalp, and invaded the dura and brain parenchyma through the emissary vein (extra-axial to intra-axial growth). Headache was the first symptom. Involvement of the brain cortex occurred later in the course of illness. Seizures and focal neurological deficit suggest brain parenchymal involvement. The other possibility is that it originated from the calvaria and then extended both intra-axially and extra-axially. However, it is also possible (given the load of lymphoma in the brain) that it originated from the dura and then extended extracranially. In the advanced stage of lymphoma, it is impossible to determine its origin; this argument is academic only.

The diagnosis of lymphoma is followed by staging, risk stratification, treatment selection, and consideration of possible treatment-related complications.⁹ Although values of serum lactate dehydrogenase (LDH), viral serology and echocardiographic findings are not mentioned, but I presume that these investigations were normal. Positive human immunodeficiency virus (HIV) serology would put the patient into the category of having AIDS, as the diagnosis of NHL in an HIV-positive individual is taken as an AIDS-defining illness.¹⁰ It is also important to know the status of hepatitis B before initiating therapy for two reasons. First, a recent meta-analysis has suggested a relationship between hepatitis B infection and the development of lymphoma.¹¹ Second, re-activation of hepatitis B virus can occur especially so if patient is receiving rituximab-based therapy.¹² Doxorubicin is the major component of all the chemotherapies given for high-grade lymphoma, an evaluation of cardiac functions before chemotherapy is a must especially for patients who are above 50 years of age.^{9,13}

The treatment of PCVL is a challenge as no guidelines exist as to the best treatment approach.^{14,15} The treatment decisions are thus based on the current knowledge of lymphoma management and experience from case reports/series. The initial intent is always to cure the lymphoma, which may or may not happen. Generally, a combination of surgery, radiotherapy, and chemotherapy is used to get the best results in PCVL. However, the most difficult part in this disease is to decide on the sequence of treatment. Curative surgery has

been performed in the past with preoperative differentials of meningioma, Ewing's sarcoma, or systemic metastasis.¹⁴ Post-surgery histopathological examination of the resected tumor in these patients had shown high-grade lymphoma. A few patients have remained well after only surgery; however, our current knowledge about high-grade NHL would preclude surgery as the only form of treatment.¹⁴ Moreover, with the involvement of brain cortex, a complete resection of the tumor is fraught with dangerous postoperative complications. Radiotherapy is another effective form of treatment for lymphoma because NHL is a radiosensitive tumor. After the biopsy diagnosis, whole brain radiotherapy is one of the treatment options for this patient. Some patients had remained well after curative surgery followed by radiotherapy; however, again, the follow-up of these cases is too short to draw any definitive conclusions.^{14–16} Rituximab, in combination with CHOP chemotherapy, has become the standard of treatment for diffuse large B-cell lymphoma.¹⁷ Elderly patients receiving R-CHOP chemotherapy for diffuse large B-cell lymphoma have significantly better event-free, progression-free, disease-free, and overall survival as compared to CHOP chemotherapy alone, and this benefit persists at a median follow-up of 5 years.¹⁷ However, in this patient, how much benefit can be gained by the addition of rituximab can only be answered by a clinical trial. Nevertheless, it should still be added if practical. In India, a less expensive generic equivalent of rituximab is available that is considered to have equal efficacy is available, though no head-to-head trial with original rituximab has been conducted.¹⁸ The most difficult question to consider in this patient is to choose CHOP or any other second- or third-generation chemotherapy regimen. A trial comparing CHOP with third-generation chemotherapy regimens did not show any difference in the response rates or survival at 3 years.¹⁹ However, in this trial patients with overt CNS disease were excluded and hence theoretically the results of this trial cannot be applied to the treatment of PCVL. The major difficulty with CHOP chemotherapy as a treatment in PCVL is that except prednisolone, other chemotherapeutic drugs have little or no penetration into the brain parenchyma. Therefore, an initial response with CHOP or R-CHOP chemotherapy may be expected because of the permeable blood-brain barrier. The chemotherapy drugs would lose their effectiveness as the disease comes under control. The drugs that achieve high concentration into the brain parenchyma are cytosine arabinoside (Ara-C) and methotrexate. Both drugs are cardinal in the chemotherapy regimens of primary CNS lymphoma.²⁰ However, these drugs are highly toxic and have considerable hematologic morbidity, especially in the elderly and in patients with poor performance status.²¹ Other drugs that penetrate the CNS and have anti-lymphoma activity are ifosfamide, thiotepe, nitrosoureas, and temozolomide.²⁰ The last thing to consider in this patient when choosing chemotherapy is the availability of supportive care at a place where the patient gets treatment. In developing countries there are always issues regarding availability of optimal supportive care for seriously ill patients.²⁰

In this patient who has presented in altered sensorium, I would initiate therapy with combination of dexamethasone and low-dose ifosfamide (a kind of pre-phase chemotherapy). I would evaluate the patient after 2–3 weeks of this pre-phase chemotherapy. This would provide the following information: (1) tumor sensitivity to pre-phase chemotherapy; (2) improvement in the sensorium; and (3) improvement in performance status. This approach to treatment may be unconventional manner of treatment;

nevertheless, I have done this in many patients in similar situations. Directly initiating full dose anti-cancer therapy in a patient with poor performance status would be risky, especially when supportive care is not optimal. We have shown in the past that infection-related mortality increased to 20% when acute lymphoblastic leukemia patients were treated with a modified Berlin-Frankfurt-Munich (BFM) regimen in our local setting²² with such high rate of infections and mortality due to dusty environments and poor availability of supportive care, besides many other contributing factors.

My next step of management in this patient would depend on the outcome of pre-phase chemotherapy. If the patient improves significantly in terms of nutritional and performance status, I would consider methotrexate-based chemotherapy (+ rituximab) followed by radiotherapy and further consolidation with Ara-C (extrapolating from a treatment approach for primary CNS lymphoma). However, if there is minimal improvement in the general condition of the patient, I would consider giving whole brain radiation (45 Gy). I would re-evaluate the patient again (disease status as well as performance status) after completion of whole brain radiation. If there is a significant improvement in the general condition of the patient, I would consider administering Ara-C-based chemotherapy, then avoiding methotrexate post-radiation because of the potential for recall phenomenon in some patients. If performance status still remains poor, I would consider monthly cycles of temozolomide with the intent of prolonging life while maintaining quality of life. I agree that once we document progressive disease, the best approach would be palliative treatment as has been done in the present case.

MEDICAL ONCOLOGISTS' EXPERT OPINION

This is a presentation of an aggressive large B-cell lymphoma that appears to have invaded through the skull into the brain. The presenting symptoms of increasing swelling followed by ulceration over several months speak to the natural progression of this aggressive disease. CNS symptoms such as headache, altered sensorium, vomiting, and seizures suggest direct invasion of the brain by local extension. The destruction of the skull on examination and scalp ulceration demonstrate the locally advanced stage at presentation and raise the possibility of this being a PCVL.

PCVL is a rare condition where the lymphoma appears to be limited to the cranial vault without evidence of systemic lymphoma. As in this case, the most common histology reported is diffuse large B-cell lymphoma. There have been only 27 previous reports of PCVL and only five with cortical invasion.^{15,23–26} More than 50% of patients with this disorder have presented with scalp swelling. B symptoms such as fevers, night sweats, and weight loss are infrequent. PCVLs are thought to occupy the subgaleal space and tend to destroy bone and invade the subdural space.¹⁵ Although the dura mater can act as a barrier for intracranial invasion, at least five cases of PCVL with involvement of the brain have been reported. The intracranial extension of this lymphoma could represent the natural progression and therefore manifest only in patients with an advanced stage at presentation as in this case. There have been reports of misdiagnosis of this condition with meningioma,²³ although MRI can help in differentiating these two conditions.

At present, there is no standard of care management for this rare presentation. Lymphomas tend to be chemo- and radiosensitive, and surgery is not believed to play a significant therapeutic role in this group of diseases. However, contrary to its use in most lymphomas, surgical resection has often been reported in PCVL, which may be due to the diagnostic dilemma at presentation. In most reported cases of PCVL with involvement of the brain, radiation therapy was used as part of the management. Responses have been seen in all five cases with brain involvement but data on long-term follow up are not available.^{15,23–26}

The standard chemotherapy for diffuse large B-cell lymphoma is a combination of rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone.²⁷ The use of rituximab has greatly improved outcomes of large B-cell lymphoma and responses also have been described in primary CNS lymphoma.^{27,28} The poor outcome in the case presented here could be related to the aggressiveness of this disease, the advanced stage at diagnosis, the overall poor condition of the patient, use of reduced chemotherapy doses, and absence of rituximab in the regimen, as well as the use of sub-therapeutic doses of radiation. The patient reported here was not able to receive rituximab because of financial concerns. This case also highlights the limited access to standard treatment options in different parts of the world.

NEURO-ONCOLOGISTS' EXPERT OPINION

A 60-year-old man presented with a right fronto-parietal parasagittal ulcerative scalp mass that had evolved over 8 months. By history and examination he was found to have posterior headaches (4-month history), nausea and vomiting, urinary incontinence (1-month history), decreased level of consciousness (2-week history), and two partial seizures that immediately preceded admission to hospital. The diagnostic evaluation in hospital included biopsy of the erosive scalp lesion that was determined by pathology to be a diffuse large B-cell lymphoma. In addition, both contrast-enhanced brain CT and MRI were performed, demonstrating tumor involving intracranial (dural disease, leptomeningeal enhancement, and moderate vasogenic edema without clear lymphomatous parenchymal disease) and extracranial (scalp and skull) compartments. Systemic evaluation that included a bone marrow biopsy and CT of the chest, abdomen, and pelvis were unrevealing for lymphoma, suggesting isolated disease to the contiguous scalp, skull, dura, and leptomeninges. Notably a lumbar puncture was not performed as part of CNS staging to assess lymphomatous involvement of cerebrospinal fluid (CSF).

Several features of this unusual and interesting case warrant comment. An intellectually challenging aspect of the case is determining site of origination of the diffuse large B-cell lymphoma. It seems highly unlikely this case is an example of a primary CNS lymphoma as these rare extranodal lymphomas (1%–2% of all cases of NHL) overwhelmingly involve brain parenchyma with (approximately 20%) or without CSF dissemination.²⁹ When systemic disease involvement is demonstrated (<3% of all primary CNS lymphomas), it typically manifests as a small tumor burden that appears not to impact CNS-directed therapy that uses a high-dose methotrexate chemotherapy platform.³⁰ In elderly men, a consideration for a testicular primary NHL should be considered and current guidelines for evaluating elderly male patients with an apparent primary CNS lymphoma recommend a testicular

ultrasound be performed. Further classification dilemma lies in the fact that this presentation may represent a primary cutaneous large B-cell lymphoma with advanced local extension.³¹ Furthermore, the authors report CD3 positivity that in conjunction with tumor location in the head raises the possibility of a primary cutaneous T-cell rich B-cell lymphoma, a very rare lymphoid malignancy with fewer than 20 reported cases.³² Alternatively, the unusual presentation of CD20 expressing transformed mycosis fungoides might also be considered in the differential diagnosis. The paucity of reported histopathologic data makes it challenging to make further determination.

Staging of the lymphoma presented in this case is also controversial. While under strict application of the Ann Arbor system this NHL would be considered stage IA_E disease,³³ we contend the case represents a stage IVA locally advanced extranodal diffuse large B-cell lymphoma, with a likely site of origination in the scalp and subsequent contiguous extension into the skull and intracranial CNS compartment. Precise staging of this lymphoma is controversial and subject to interpretation, which further underscores the limitations of the current NHL staging system. Optimal treatment (assuming a reasonable performance status on hospital admission) would use a combination of systemic chemotherapy and radiotherapy as in the present case; however, management would alter if CSF analysis by flow cytometry and cytology were positive. As the original MRI of brain suggested leptomeningeal involvement, we would have additionally treated the CSF compartment and likely would of recommended initial whole brain radiotherapy followed by R-CHOP or R-EPOCH for six cycles. However, given the toxicity of whole brain irradiation, it would be acceptable to utilize involved-field external beam radiotherapy with adjuvant multi-agent chemotherapy. In both treatment scenarios intra-CSF therapy would be administered concurrently with systemic chemotherapy. The decision between utilizing whole brain irradiation or involved-field external beam radiotherapy would be made based on treatment objectives and a determination of the risk-benefit ratio for an individual patient. Another alternative to the above-proposed adjuvant therapy would be a combination of high-dose methotrexate (HD-MTX) and R-CHOP.³⁴ This approach would provide adequate systemic and CNS exposure and would potentially eliminate the need for intra-CSF chemotherapy. However, we recognize that there are no evidence-based guidelines for these recommendations but believe the high risk for leptomeningeal and parenchymal brain disease warranted upfront use of whole brain irradiation/involved-field external beam radiotherapy and either intra-CSF chemotherapy or systemic HD-MTX. An additional value to upfront radiotherapy would be the high likelihood of markedly reducing the original large tumor mass and thereby facilitate closure of the erosive scalp lesion.

Treatment of cancer in developing countries is challenging for many reasons, not the least of which is the availability of expensive agents such as rituximab that have documented benefit in diffuse large B-cell lymphoma. The rapidity of recurrence suggests refractory disease and in a patient deemed salvageable, an alternative anti-lymphoma regimen such as RICE or R-DHAP would be recommended and if a complete response could be achieved both in brain and systemically, consolidation with autologous or allogenic peripheral stem cell transplantation would be customary practice in the United States. The decision to institute salvage therapy in a patient with refractory diffuse large B-cell lymphoma is complicated and determined by patient performance status, an estimation of treatment benefit, desire by

the patient, and available resources permitting treatment. In a patient with rapidly relapsing disease and likely CNS extension, supportive care only would be an appropriate choice of therapy.

NEURO-ONCOLOGIST'S EXPERT OPINION

This patient is a 60-year-old man with progressive enlargement over 8 months of a lesion involving the scalp in the right frontal-parietal-occipital region, which was associated with mild superficial pain, headache, emesis, and urinary incontinence. Late in the course of the presentation, he noted mental status changes and focal seizures. CT and MRI scans revealed extensive bone erosion and destruction, along with underlying infiltration and edema within the brain. After biopsy, the subsequent histological diagnosis was consistent with NHL, diffuse large B-cell type, positive for CD3 and CD20. The systemic evaluation was negative for evidence of lymphoma. He responded to treatment with chemotherapy and radiation therapy.

Lymphoma can involve the scalp, cranial vault, leptomeninges, and brain as a metastatic process, or as a primary tumor.^{14,35–37} Metastases into the scalp and cranial vault are much less common than spread into regional and systemic lymph nodes, bones other than the skull, and the leptomeninges surrounding the brain. The clinical presentation usually involves an enlarging scalp mass, localized pain and headache, fatigue, and various neurologic symptoms (eg, seizures, focal weakness).³⁸ For primary lymphomatous tumors of the scalp and cranial vault, the clinical signs and symptoms are quite similar.^{14,25,39–44} Most patients will present with an enlarging subcutaneous scalp mass, along with symptoms of headache, localized scalp pain, fatigue, and neurological complaints if the underlying brain is involved, such as seizures, confusion, and focal weakness. Therefore, based on the clinical features, the clinician cannot tell if the lymphomatous involvement of the scalp and cranium is from a metastatic process or a primary tumor. The systemic workup, including CT or MRI of the chest, abdomen, and pelvis, bone marrow aspiration, and either a total body PET scan (if available) or nuclear medicine scan, will be needed to verify the presence of systemic primary disease.

The current patient's clinical history was compatible with primary NHL of the scalp and cranial vault, and was similar in presentation to many other cases that have been reported.^{14,25,39–44} This is a very rare location for primary lymphoma, having been described in less than 40 cases in the world literature.¹⁴ Patients have ranged in age from 19 years to over 70 years, with a mean age of 60 years. There has been an equal male-to-female ratio. The vast majority of the patients were immunocompetent (approximately 88%). By CT and MRI scan, most of the patients had underlying cranial vault bone erosion and osteolysis; less commonly, the skull showed hyperostosis or remained intact. Histologically, the most common type of NHL was diffuse large B-cell, although low-grade and intermediate-grade B-cell lymphomas also have been described.

The CT and MRI scans of the current patient showed the tumor causing extensive bone erosion and destruction of the underlying cranial vault, extension into the leptomeninges, and compression and invasion of the underlying brain. Similar neurological involvement is,

in fact, not uncommon in patients with lymphoma of the scalp and cranial vault, leading to compression, irritation, and invasion of the underlying brain in many cases. Irritation of the cerebral cortex, loss of inhibitory GABAergic inputs, and injury to nearby neurons and glial cells are responsible for the focal and generalized seizure activity noted in many of the case reports, including the current patient.⁴⁵ First-line treatment of tumor-related focal or generalized seizures would consist of levetiracetam, which has proven efficacy against primary brain tumors, as well as metastatic brain disease.^{46,47} In addition, levetiracetam does not interact with the liver cytochrome P450 system, and has minimal interaction with other drugs, including chemotherapy. Similar mechanisms of CNS injury and dysfunction can lead to the other common neurological symptoms and signs that have been reported, such as mental status changes, confusion, and focal weakness. There is potential for neurological improvement with aggressive treatment of the lymphoma.

The first line of treatment should be neurosurgical intervention, either to biopsy the mass in the scalp and bones of the cranial vault, or to perform a more definitive resection of the tumor.^{14,41} There is no clear “best approach” in the literature, since many patients have done well with only a biopsy, while others have had more aggressive surgical resections.^{16,25,39,40,42,43} In general, the more extensive surgical resections were used in patients with widespread disease, in which the scalp, bones of the cranial vault, leptomeninges, and underlying brain were all affected. The neurosurgical procedure will provide tissue for the definitive diagnosis of NHL and immunophenotyping, and may also substantially lower the tumor burden for subsequent chemotherapy and radiation.

The current patient received five cycles of CHOP, and had a fairly good response, with clinical improvement and tumor shrinkage on CT follow-up. Most of the patients reported in the literature also received chemotherapy (CHOP or similar regimen) and had positive responses.¹⁴ I would suggest starting chemotherapy as the first form of treatment after recovery from surgery, using CHOP (and rituximab, if possible) as the regimen of choice, every 3–4 weeks for six cycles. For patients with a small disease burden, or who have sensitive tumors, chemotherapy may be enough to completely eradicate visible disease. For very large tumors, or those with some resistance, upfront chemotherapy may at least reduce the tumor volume prior to the onset of radiation.

For patients that have significant residual disease after the completion of chemotherapy, or who show evidence for chemotherapy resistance (like the current patient) radiation will be required. After five cycles of CHOP, the current patient developed a new $3 \times 3 \times 1.5$ cm nodule in the frontal-temporal region, suggesting the development of resistance. He was given palliative radiation to the whole brain, consisting of 8 Gy in a single fraction, which did result in shrinkage of the new nodule. Radiotherapy also was used for most of the cases reported in the literature.¹⁴ However, most of them used a more conventional dosing regimen, with fractionated treatment over 5–10 days. Unless the patient has severe neurological compromise and/or a poor performance status, I would suggest a radiation regimen of 20–30 Gy over the course of 5–10 treatment days.^{36,37}

Primary scalp and cranial vault lymphoma is a rare form of NHL, which should always be included in the differential diagnosis of an enlarging scalp mass. Most patients respond well

after receiving an aggressive, multi-modality treatment regimen that includes surgery, chemotherapy, and radiation therapy. Using this approach, some patients have remained free of recurrent disease for over 5 years.¹⁴

NEURO-ONCOLOGISTS' EXPERT OPINION

PCVL is an extremely rare presentation, with only 26 prior reported cases in the literature. PCVL in the immunocompetent patient is even rarer, with only 14 reported cases in the literature. Similar to this case, most patients with PCVL present with painless scalp swelling, headaches, and eventual focal neurologic symptoms. Most PCVLs are B-cell lymphomas and are treated with regimens similar to those used for systemic non-Hodgkin B-cell lymphomas. However, given the rarity of these tumors, there is no clear standard of care therapy for PCVL.

This particular case describes a tumor with apparent extra-CNS origin at the scalp and the skull with extension inward to the meninges. Given the lack of lymph node and lack of demonstrated systemic involvement this tumor presumably came primarily from the scalp with aggressive inward invasion. Workup for systemic disease should include a bone marrow biopsy and CT of the chest, abdomen, and pelvis as done in the presented case. Additionally, for diagnostic and staging purposes, it is also advised to complete an ocular slit lamp exam to assess for ocular lymphoma, lumbar puncture (if safe) to look for CSF spread, and MRI of the whole spine; PET imaging might also be performed to look for areas concerning for malignancy.

Histologic testing is essential in establishing a diagnosis; however, the immunohistochemistry is of particular importance in diagnosing PCVL. In this case, the biopsy was suggestive of NHL and therefore triggered further immunohistochemistry testing. The tissue was diffusely positive for CD20, which confirmed the diagnosis of diffuse large B-cell lymphoma, and the negative CD30 opposed the diagnosis of Hodgkin lymphoma. CD3 (a T-cell marker) was also positive in this case; however, this can be seen frequently in B-cell lymphomas. Although the CNS was anatomically involved in the patient's disease, the blood-brain barrier in this affected area was altered with the subsequent leptomeningeal and parenchymal invasion (which was further evidenced by the gadolinium uptake). Because of the disruption in the blood-brain barrier, theoretically the CNS should be exposed to therapies administered systemically.

Diffuse large B-cell lymphoma systemically is treated with anthracycline-based chemotherapy. The standard of care is R-CHOP for systemic treatment. No similar standard of care exists for CNS prophylaxis in the treatment of systemic disease. It is known that about a third of systemic diffuse large B-cell lymphoma patients will have CNS involvement at some point in their disease course. Typically, the treating physician stratifies the patient as either high or low risk and prescribes CNS-directed prophylaxis appropriately. Neither the guidelines for risk stratification or the drug of choice are standardized, creating significant variability in both chemotherapeutic agent used and drug administration schedule. Most commonly, patients are treated with either intrathecal methotrexate, intrathecal cytarabine, or high-dose intravenous methotrexate. There are a number of diagnostic characteristics that

clinicians consider to be high risk. These include International Prognostic Index (IPI) along with serum lactate dehydrogenase (LDH), number of extranodal sites (2+), or specific site involvement (bone marrow, testes, breast, or parameningeal). Prediction of later CNS disease has taken into account these characteristics alone and in combination but with still no standard formula to determine rate of CNS recurrence.

Given this patient's presentation, treatment with upfront R-CHOP administration is rationale (although this patient was not able to get rituximab due to financial constraints). In addition to this I would have considered focal radiotherapy given the disease response seen with other PCVLs when given in conjunction with chemotherapy. Although there are no clear evidence-based data on agent or dosing, given the leptomeningeal and parenchymal invasion I also would have considered high-dose intravenous methotrexate (in doses greater than 3.5 mg/m²) for optimal CNS prophylaxis.

In previous follow-up of the aforementioned 14 patients, 75% achieved complete remission for an average of approximately 7 months' duration with the use of R-CHOP and, for most, targeted radiation. Given the high rate of local relapse, patients who are affected should be closely monitored with imaging of the primary affected area performed about every 8–12 weeks for at least the first year following initial treatment. Additionally, if disease progression or recurrence is observed, the patient should undergo re-staging with the previously mentioned modalities.

NEURO-ONCOLOGIST'S EXPERT OPINION

This is a patient who presented with scalp swelling and progressive decline in mental status, headaches, vomiting, seizures, and urinary incontinence. The scalp swelling was associated with local destruction of bone along the vertex and in the right calvarium. Evaluation revealed the presence of diffuse large B-cell lymphoma.

This patient's symptoms (headaches associated with vomiting and urinary incontinence) are those of increased intracranial pressure. This raises the differential diagnosis of extra-axial with or without intra-axial CNS involvement of this neoplasm. The head CT scan revealed cerebral edema with no obvious focal area of abnormality. The brain MRI (images not provided) confirmed the presence of extra-axial (dural, skull, and meningeal) nodular enhancement without obvious intra-axial neoplastic involvement.

This patient presented with signs and symptoms of increased intracranial pressure, prompting the need for a head CT scan that confirmed the presence of cerebral edema. The presence of a scalp lesion and bony erosion argues against an infectious process and for a neoplastic process. Differential diagnosis includes myeloma, lymphoma, carcinoma (though unlikely to produce diffusely lytic lesions), and an infectious process (again unlikely given the slow progression of symptoms and the relative lack of severity of the illness).

Symptom management takes precedence. Corticosteroids are indicated for treatment of increased intracranial pressure. With the understanding that lymphomas, including myeloma, may have a cytotoxic response to corticosteroids, biopsy should be done as soon as possible.

MRI will provide full delineation of tumor burden extracranially, intracranially, and intraparenchymally. This patient had evaluation of the skull, dura, and meninges and evidence of parenchymal invasion. MRI of the spinal axis (cervical, thoracic, and lumbar spines) without and with contrast is of help in determining the presence of meningeal disease and/or spinal cord parenchymal disease. Unless contraindicated due to intracranial mass effect, lumbar puncture may be performed to evaluate for meningeal metastasis if imaging is non-diagnostic despite clinical suspicion.

Lymphoma can involve the CNS by a variety of mechanisms. Primary central nervous system lymphoma is, by definition, a NHL confined to the CNS, meninges, or intra-ocular contents without detectable involvement elsewhere. This patient does not have a primary CNS lymphoma as there is involvement of the dura, the skull, and extracranial structures (ie, sub-cutaneous tissue). Systemic lymphomas can metastasize to the CNS, primarily involving the meninges, without direct invasion. In this case, however, there is direct invasion of the CNS from a primary focus affecting bone and subcutaneous tissue.

Disease outside the nervous system (in this case, dural, skull, and subcutaneous tumor) will be susceptible to standard anti-neoplastic therapies, such as R-CHOP. However, the components of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) have limited or no penetration of the CNS, or (in the case of corticosteroids) limited duration of cytotoxic action. Patients may experience a limited response to rituximab before tumor response closes the blood-brain barrier. When treating primary CNS lymphoma or secondary intraparenchymal or meningeal lymphomas, antineoplastic agents penetrating the blood-brain barrier in therapeutic levels, such as high-dose methotrexate, are typically used. Intrathecal chemotherapy, such as methotrexate, cytarabine, or liposomal cytarabine, are also useful in the treatment of meningeal lymphoma. However, therapeutic CSF levels of methotrexate are usually obtained following a systemic dose of 3 g/m² or higher and may result in the clearance of meningeal lymphoma without the need for intrathecal chemotherapy.

DISCUSSION

As presented, primary cutaneous NHL is an uncommon entity, with an overall incidence of 1 in 1.5/100,000.¹ Primary cutaneous NHL is the third most common extranodal lymphoma, closely following gastrointestinal and head and neck lymphomas. About 75% of all primary cutaneous NHLs are of T-cell origin and 25% are of B-cell origin. Most primary cutaneous B-cell lymphomas reported have involved the head and neck. Primary cutaneous NHL of the scalp itself usually runs an indolent course with the primary presentation as a lesion or swelling on scalp, but eventually may progress to involve the underlying skull and dura. Thereby it can present with late onset focal neurological deficits, as in our case. Primary scalp lymphoma should be differentiated from the primary malignant NHL of cranial vault/skull, as is discussed above by our neurooncology colleagues.

By definition, primary bone lymphoma is a solitary mass lesion with no evidence of disease at other sites and no systemic dissemination within 6 months of the detection of tumor.⁴⁸ As also discussed, primary bone NHL is extremely rare with a reported incidence of only 3%–

4%.⁴⁹ This entity, originating from the vault, may extend outside the cranium first and within the cranium subsequently; at presentation, more than half of the patients report with a scalp mass rather than any neurological sign. The other main clinical-radiological differences between primary cutaneous NHL of the scalp and primary NHL of the cranial vault include a shorter duration of symptomatology and early onset of focal neurological deficits, large soft-tissue mass, and extensive osteolytic lesions in primary NHL of the cranial vault.^{43,50} Still, it is PCVL that is more frequently associated with intracranial (extradural) extension.⁴⁹ Lymphomas of the cranial vault usually involve the pericranium, meninges, and subcutaneous tissues. Cranial vault lymphoma is more commonly associated with intracranial extradural extension. All of these features were seen in the present case; however, with diffuse ulceration of almost two thirds of the scalp, which is rare in vault lymphoma. The underlying skull vault was also extensively destroyed by osteolytic lesions in parallel to the scalp swelling and ulceration. As additionally considered by our co-authors, another differential entity is a primary CNS lymphoma, which has involved the skull vault and then subsequently the scalp. This cannot be ruled out because of the history of fall and cranial injury 4 months prior to the development of scalp swelling, lending credence to the hypothesis that primary CNS lymphoma might have infiltrated through the fractured skull vault. Other important clinicopathologic and radiological differential diagnoses include protruding tumorous angiolymphoid hyperplasia with eosinophilia (ALHE), Kimura's disease of the scalp, pseudolymphoma, cranial vault meningioma, osteomyelitis, turban tumor, and metastasis.^{51,52}

Histologically, all reported lymphomas of the cranial scalp or vault are of B-cell origin. Demographically, most of cases are reported in middle-aged (similar to our index case) and elderly women.

Most primary cutaneous NHLs are hyperdense on unenhanced CT and show marked enhancement on post contrast studies. In contrast, CT features of primary bone NHL are nonspecific. Characteristic features are a permeative growth pattern with very little cortical destruction.²⁶ Periosteal reaction is occasionally seen. Although lymphomas usually reveal a homogenous appearance, most reported cases of the cranial vault lymphoma have demonstrated heterogeneous hyperdensity.⁵³ An associated large soft-tissue component is again very common with extension of mass in the extradural compartment and galeal compartment. Post contrast studies show mild contrast enhancement. Calcification is usually absent.⁵⁴

MRI is important for evaluating locoregional spread and gauging involvement of the bone marrow and leptomeninges as in our index case, or of the dural venous sinuses.⁵⁵ Gallium scanning can rule out or confirm extracutaneous involvement and the presence or absence of activity in cases of gallium avid lymphomas is helpful in indicating the nature of residual soft tissue masses following chemotherapy/radiotherapy.

Only 15%–25% of cutaneous lymphomas show extra cutaneous manifestations at time of diagnosis. The prognosis is relatively good, since the average survival time from diagnosis is 12–14 years,⁵⁶ but when the site is the skull vault/scalp, the prognosis is uncertain after

intracranial extension is seen. Still, any involvement of the cerebral structures by direct invasion or by leptomeningeal seeding should indicate a less favorable prognosis.

As discussed, the treatment for extranodal NHL, for both scalp and vault, usually includes a doxorubicin-containing regimen like CHOP, followed by radiation therapy. We started the patient first on chemotherapy because there was gross ulceration of the scalp along with massive bone erosion without overt bleeding, and allowed 3 weeks between cycles to assess for sufficient tumor regression, healing of the scalp, bone reformation, and meningeal preservation. Alternatively, chemotherapy without subsequent radiation therapy and radiation therapy alone can be used in carefully selected cases.⁵⁷ Survival in most cases has been less than 24 months, with clinical stage being the most important prognostic variable in predicting overall survival.

CONCLUSION

We report here a case of NHL of the scalp where definitive diagnosis was made based on histology. The case has been reported because of its rare occurrence, presentation, and quandary in management. A differential diagnosis of primary lymphoma of the skull vault and primary CNS lymphoma with extracranial extension should always be considered when such a lesion is encountered in elderly patients, and may guide treatment decisions. We posed clinical questions as to the origin of the NHL, and subsequent guidance on sequencing available multidisciplinary treatment modalities, and recommendations as to further treatment upon progression of disease. From a medical oncologic and neuro-oncologic perspective, the likely origin was diffuse large B-cell lymphoma from the scalp. Ideally anti-CD20–based combination chemotherapy if available, as well as options with backbones of leukemic regimens or DNA alkylating agent temozolomide are the preferred treatments. From a radiation oncologic perspective, palliative treatment is used to alleviate local and debilitating symptoms stemming from the mass effect of this tumor burden.

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Gloria J. Morris, MD, PhD Current Clinical Practice Feature Editor

Figure 1.
CT scan brain. (A) Hypodense lesion in the vertex and bilateral parietal regions of the skull with gross brain edema. (B) There is infiltration of scalp with partial ulceration more on the right side including occipital area. (C) Extensive cranial bone erosion.

Figure 2.

(A-C) MRI of the brain revealed T1 hypointense, T2 isointense, heterogeneously enhancing nodular soft tissue (maximum thickness 3 cm), with predominantly extradural and extracranial components, extending across the circumference of right side, vertex and bilateral high fronto-parietal convexities of the skull with destruction of right high fronto-parietal cranial bone. In addition, there is leptomeningeal enhancement in right cerebral convexities as well as suggestion of parenchymal invasion in high parietal region with midline shift to right.

Figure 3.

(A, B) Contrast-enhanced brain CT after five cycles showed reduction in the scalp swelling. Bone destruction was reduced to great extent and there is reformation of the skull bone. There is an enhancing soft tissue lesion, $3 \times 3 \times 1.5$ cm in the scalp in the right temporal and frontal area with underlying cerebral edema and underlying bone erosion.