Feeling Green

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Case Presentation: Dr. Aisha Ghare

A 4-year-old male was admitted to the pediatric medicine service after a 5-day history of severe holocephalic headaches and an episode of emesis the day prior to admission. The headaches were progressive in severity, occurring in the early morning and often walking him up from sleep. No seizure activity, focal deficits, or infectious symptoms were reported by parents. His past medical history was significant for diagnosis of acute monocytic leukemia (AML) 1 year previously. Bone marrow karyotyping and interphase fluorescence in-situ hybridization at the time of initial presentation revealed AML with 11q23 abnormalities at the *MLL* (mixed lineage leukemia) gene, with t(1:17) and ins(10;11). He received four cycles of chemotherapy on the Children's Oncology Group (COG) protocol AAML1031,[1] with a line infection complicating his third cycle. After his fourth cycle, he was discharged home. Throughout his initial diagnosis and up to the time of current presentation – 6 months after his last chemotherapy cycle – he did not demonstrate any signs or symptoms of neurologic abnormality and was central nervous system (CNS)-negative.

His vitals were within normal limits, and a systemic physical examination was unremarkable. On neurologic exam, there were no noted cranial-nerve deficits or papilledema. No objective deficits in power, sensation, and cerebellar testing were elicited, and no upper motor neuron signs were elicited. Initial bloodwork showed no abnormalities.

Discussion: Dr. Andrade

The history provided of a 4-year-old child post-chemotherapy – thus likely in an immunosuppressive state – presenting with a clinical picture of early morning vomiting and headache suggests raised a process of raised intracranial pressure (ICP). There are no focal signs indicating a clear localization of the lesion, instead the findings indicate a progressive and diffuse process. Typically, headache, vomiting, and gait disturbances are seen in posterior fossa occupying lesions, whereas supratentorial tumors typically present with focal seizures, motor, language, or sensory abnormalities.

The differential diagnosis of immunocompromised children with posterior fossa mass can be divided into three broad categories: neoplastic, infectious, or vascular.

Regarding vascular etiologies, cerebral venous sinus thrombosis (CVST) is a common complication of children with leukemia, specifically those who are prothrombotic due to the lymphoproliferative disease or those who have received asparaginase as part of their treatment (e.g. patients with ALL). CVST can present with nonspecific signs of increased ICP. Usually, venous infarctions are associated with focal seizures and cortical deficits. Other vascular complications such as acute ischemic stroke, intracerebral hemorrhage, and posterior reversible encephalopathy syndrome are rather acute and present with sudden onset of focal deficits, rather than the progressive headaches we see in this case.

The next possibility is an opportunistic infection, which can be seen in children receiving chemotherapy. The most common ones include fungal infections such as Aspergillus and Candida. During chemotherapy-induced neutropenia, colonization with fungi is considered as a major risk factor for a subsequent fungal infection. Usually, these patients present with a more severe presentation and are also associated with systemic aspergillosis. The clinical picture would include confusion and focal neurological deficits. Multiple enhancing lesions can be seen on contrast CT and MRI.

Lastly, and most likely differential, is neoplasm. CNS leukemic infiltration can present in one or more of the following intracranial forms: (1) meningeal disease, as "carcinomatosis meningitis"; (2) intravascular tumor aggregates throughout the brain as "carcinomatous encephalitis"; (3) focal solid extramedullary hematopoietic tumors called "chloromas," also termed myeloid sarcoma (MS); and (4) leukemic blasts in the cerebrospinal fluid (CSF), typically defined as the presence of at least five leukocytes/μl of CSF, with leukemic blast cells apparent in a cytocentrifuged sample of cerebrospinal fluid, or the presence of cranial-nerve palsies.[2]

Central nervous system myeloid sarcoma (CNS-MS) is a rare manifestation of AML, chronic myeloid leukemia (CML), and other myeloproliferative malignancies. Intracranially, MSs are often contiguous with the meninges and ependyma but can rarely present intraaxially. When AML manifests as a solid tumor outside the bone marrow, it can be mistaken with meningioma, B cell lymphoma and intracranial metastasis. MS can express B cells antigens and potentially lead to a histologically misdiagnosis of CNS lymphoma. Another consideration in this case would

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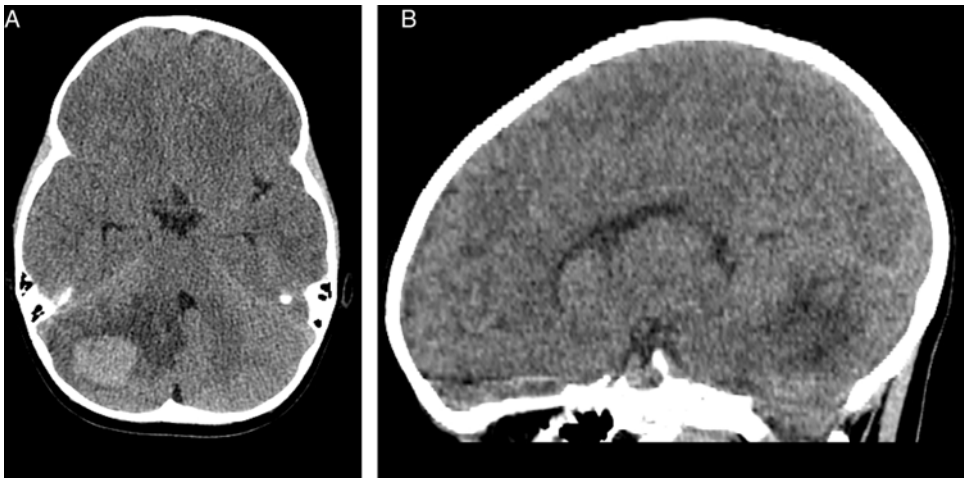

Figure 1: *Axial noncontrast CT scan reveals a hyperdense mass in the right cerebellar hemisphere with moderate surrounding vasogenic edema causing effacement of the fourth ventricle (A) and right cerebellar tonsillar descent resulting in crowding of the foramen magnum (B).*

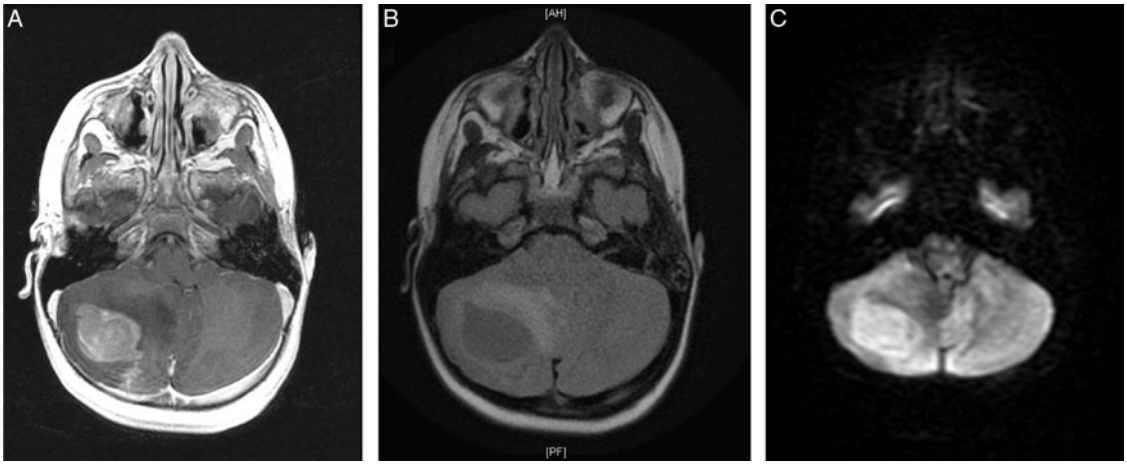

Figure 2: *MRI confirmed a lesion in the right cerebellar hemisphere, with prominent contrast enhancement, with a linear focus of enhancement at the margin (A). FLAIR sequences showed moderate surrounding edema, crowding of the basal cisterns, and mass effect on the fourth ventricle (B). Axial multiplanar gradient echo sequences showed few punctate foci of susceptibility within the lesion in keeping with calcification or blood product (not shown) and DWI (C) and ADC images showed diffusion restriction, indicating hypercellularity (not shown).*

include primary CNS lymphoma. Given the clinical signs of raised ICP and a broad differential, I would like to see neuroimaging, and if there are no masses that are a contraindication to a lumbar puncture, then proceed with the latter to assess results of CSF analysis. A bone marrow analysis would be useful to assess whether the patient has active disease again.

Investigations: Dr. Ghare and Dr. Kiwan

Bone marrow workup showed no morphologic evidence of marrow involvement with AML.

An unenhanced CT scan demonstrated a hyperdensity in the right cerebellar hemisphere with surrounding edema and right cerebellar tonsillar descent resulting in crowding of the foramen magnum (Figure 1). MRI confirmed a lesion in the right cerebellar hemisphere, with prominent contrast enhancement, with a linear focus of enhancement at the margin (Figure 2A). Fluid-attenuated inversion recovery (FLAIR) sequences showed moderate surrounding edema, crowding of the basal cisterns, and mass effect on the fourth ventricle (Figure 2B, C). Axial multiplanar gradient echo sequences showed few punctate foci of susceptibility within the lesion in keeping with calcification or blood product (not shown), and diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) images showed diffusion restriction, indicating hypercellularity.

Radiological differential diagnosis of the lesion included chloromas, cerebellar astrocytoma, medulloblastoma, and atypical teratoid/rhabdoid tumor.

Discussion: Dr. Andrade

The bone marrow findings show that the patient does not have active AML; however, this would not preclude development of MS, as these can manifest following clinical remission. Given the

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imaging findings, and interpretation from neuroradiology colleagues, I suspect that this lesion may be an MS. At this point, I would consult my neurosurgical colleagues on the possibility of a biopsy to provide a tissue diagnosis, and/or full resection of the lesion.

Neurosurgery: Dr. Ranger

The Pediatric Neurosurgery team was approached by the Pediatric Oncology team for consideration of a biopsy, and possibly a resection. Empiric treatment of the lesion as chloroma was felt to be inappropriate; if the tumor was unrelated to his leukemia, it would likely need to be fully resected to confer the best survival advantage.

After discussion among the Oncology Team, Neurosurgery and Neuropathology, it was felt that the most prudent course would be to pursue a biopsy and send specimens intraoperatively for frozen sectioning for a preliminary tissue diagnosis and flow cytometry and base further resection on the results of the biopsy.

The patient underwent a suboccipital craniotomy, and after exposing through the dura and normal cerebellar tissue, we landed on the mass. It had a rather firm capsule and had a pale appearance overall with beige coloration and only a mild degree of vascularity. Several specimens were submitted for intraoperative consultation to neuropathology, with additional sections for permanent sections and flow cytometry.

Pathology: Dr. Langdon

Staff neuropathologist, Dr. Hammond, examined the intraoperative sample. Smear preparations and frozen sections revealed a small blue cell tumor, favoring hematopoietic lineage (Figure 3A).

On flow cytometry, a population of lesional cells representing approximately 81% of the total were positive for CD117 (dim), CD33 (bright), CD64, CD36 (dim), CD4 (dim), HLA-DR, and CD38 and negative for CD34, CD19, CD10, CD13, CD16, CD14 (MY4 and Mo2), CD7, CD3, and CD5. These features were consistent with extramedullary involvement by AML.

On routine stains, the specimen demonstrated a densely cellular mononuclear neoplasm (Figure 3B). Neoplastic cells possessed large nuclei with variably prominent nucleoli and folds. Auer rods were noted in select cells. The brain:tumor interface was relatively well defined (Figure 3C) as shown with glial fibrillary acidic protein (GFAP) staining, but with sparse infiltrates of single cells into adjacent parenchyma. Immunohistochemistry (IHC) demonstrated abundant expression of CD4 (Figure 3D), CD163, and CD68 (Figure 3E). Selective and lighter expression of CD117 and myeloperoxidase (MPO) (Figure 3F) was identified in a small minority of cells. CD34 highlights the background vasculature, and TdT was not expressed (not shown). The final diagnosis was chloroma.

Patient Follow-Up: Dr. Ghare

When the preliminary interpretation was consistent with a chloroma, the neurosurgical team proceeded with closure of the dura and craniotomy, not resecting any further tissue. The patient recovered well from surgery, without postoperative complications. Once the diagnosis was confirmed, the patient was started on chemotherapy with high-dose fludarabine and cytarabine, for three cycles. His first postoperative MRI one month later showed a small area of poorly defined enhancement in the right cerebellar hemisphere, improved from his initial MRI. However, a repeat scan two month postoperatively demonstrated slight increase in the size of the enhancing nodule and there was concern of recurrence. The patient was given 2000 cGy in 10 fractions. Both a peripheral smear and bone marrow analysis demonstrated leukemic blasts, and he was started on a salvage regimen of Ara-C/idarubicin and gemtuzumab. Unfortunately, he went on to have an opportunistic pneumonia, with associated pleural effusion and bacteremia. He was started on broad spectrum antibiotics but continued to remain febrile and had decreasing level of consciousness. A day later, he had further deterioration, with stiffening and posturing, and dilated and unreactive pupils. It was felt that he likely had an acute CNS event; family did want any investigations or aggressive intervention and wanted to focus on comfort care. The patient died a few hours later and family declined an autopsy.

Topic Review: Dr. Ghare

MS is a rare solid tumor made of myeloblasts or immature myeloid cells in an extramedullary site or in bone.[3] It was first described by Burns in 1811 as "chloroma" from the Greek word "chloros" (green), as these tumors often have a green tint due to the presence of MPO. MS has also been termed extramedullary myeloid tumor or granulocytic sarcoma. Diagnosis often precedes, coincides, or follows hematologic neoplasms (HNs) such as acute myeloid leukemia, chronic myeloproliferative neoplasms, chronic myelogenous leukemia, polycythemia vera, myelofibrosis, essential thrombocythemia, and myelodysplastic syndrome. AML is the most common associated malignancy, accounting for 46.3% of cases.[4] In 2003, Audouin et al.[5] described four different patterns of MS development in patients with AML: (1) they may develop during the active phase of leukemia; (2) they may develop concurrently with known chronic myeloproliferative disorders; (3) they may manifest as a relapse after months or years of clinical remission of AML, especially after bone marrow transplantation; and (4) they may precede the AML diagnosis to be detected in previously healthy patients who have a normal peripheral blood cell count and who have no blast infiltration of the bone marrow; 80–87% of these patients will go on to develop AML within 10 months.[6,7] MS occurs in 1.4–9% of AML cases, and in 3–8% of all patients with HNs.[8]

MS typically presents in the orbit, skin, soft tissue, bone, lymph nodes, and the gastrointestinal tract.[8] CNS-MSs are rare, occurring in 0.3–6% of patients with HNs, and are more prevalent in males than females, likely reflecting the gender distribution of myeloid leukemia.[6,7] CNS-MS is often contiguous with the meninges and ependyma, but can rarely invade the brain parenchyma and thus may appear as an intraaxial mass. MS is more common in the spinal cord (54%) than in the brain (40%), and rarely in both (6%); when it occurs in the spinal cord, tumors are usually epidural and cause cord compression.[8] In the brain, MS frequently involves the parenchyma (43–54%), followed by dura (41%).[2,8] Though deemed rare, several large treatment trials and case series have been published in the literature reporting CNS-MS.[9–17] In the Children's Cancer Group (CCG) protocols for intensive-timing chemotherapy treatment for AML,[10] the authors

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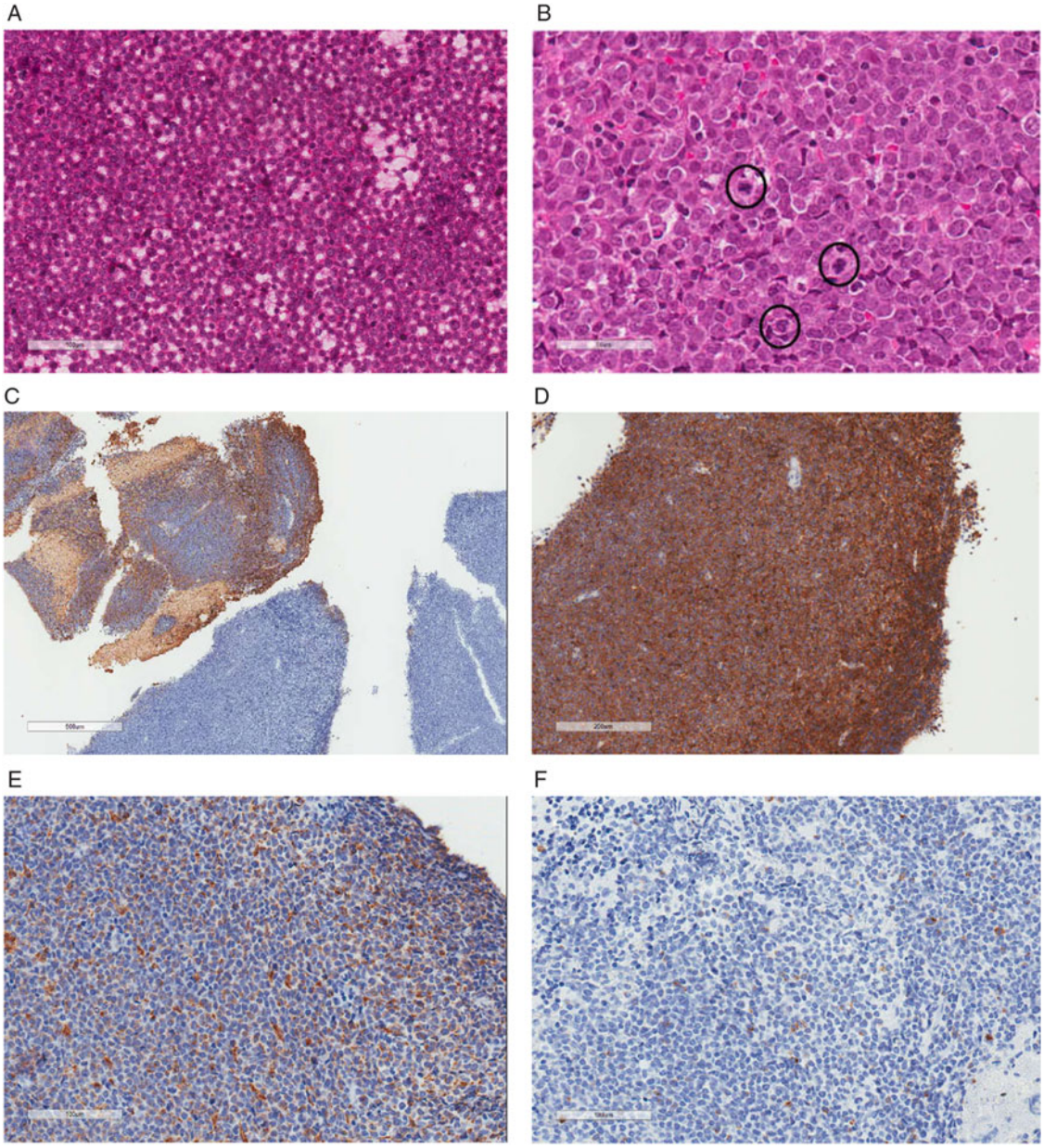

Figure 3: *Smear preparation and frozen demonstrated small blue cell tumor, favoring lymphoid tissue (A). On routine stains, the specimen demonstrated a densely cellular mononuclear neoplasm, with variably prominent nucleoli and folds (B). The brain:tumor interface was relatively defined (C) as shown with GFAP staining, but with sparse infiltrates of single cells into adjacent parenchyma. Immunohistochemistry demonstrated abundant expression of CD4 (D), CD163, and CD68 (E). Selective and lighter expression of CD117 and myeloperoxidase (F) was identified in a small minority of cells. Diagnosis was consistent with myeloid sarcoma.*

reported that of the 1459 patients, 19 (1%) had CNS-MS, while the NOPHO (Nordic Society of Pediatric Hematology and Oncology)-AML 2004 trial of 315 patients found 22 (7%) had CNS disease but only 2 had MS in the dural/epidural space.[9]

The pathogenesis of CNS infiltration is unclear; it is hypothesized that leukemic cell infiltrates are capable of migration from the bone marrow of the periosteum to the dura, into the underlying brain parenchyma once there is disruption of the pial–glial barrier.[18] However, this theory does not explain the development of MS lesions deep in the brain parenchyma.

Radiologic features of CNS-MS are nonspecific: on CT, lesions typically present as anisodense or hyperdense mass, with marked homogenous contrast enhancement. MRI reveals a hypo to isointense on T1- and T2WI with homogenous enhancement following gadolinium administration.[2,16] Using the NOPHO-AML registry, Ranta et al. evaluated the neuroimaging findings in 22 of 34 children with AML and CNS involvement at diagnosis. They found that five had CNS involvement by imaging, two had solid contrast enhancing intracranial tumors, one had an orbital tumor with intracranial

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contrast enhancement, and two had spinal tumors.[19] Rare parenchymal cases have shown peripheral ring enhancement. Thus, CNS-MS may mimic CNS lymphoma, glioblastoma, and if dura-based, meningioma and schwannoma. In the spine, CNS-MS may show nerve root thickening, mimicking nerve sheath tumors.

Definitive diagnosis depends on pathology, immunohistochemistry (IHC), and flow cytometry. Routine staining will show a characteristic Indian file pattern, and the MIB-1 monoclonal antibody index is usually high; the predominant cell type will determine classification into granulocytic, monoblastic, and myelomonocytic. An appropriate IHC panel would include CD43, CD34, lysozyme, MPO, CD68 (or CD163), CD117, CD3, and CD20.

CNS-MS is typically managed through a combination of local surgical resection, chemotherapy, and radiation; however, the utility and safety of surgical resection is still controversial. Some advocate surgical resection only if the MS is spinal and causing cord compression, especially as complete surgical resection is difficult due to the extensive infiltration of MS into surrounding tissues.[16] There are no established guidelines for the management of CNS-MS, given its rare occurrence, however, a review of 45 cases of CNS-MS by Struhal et al., looking at systemic/intrathecal chemotherapy, radiation, and surgery, found that there was no superior modality among combination of treatment options available, but suggested that systemic chemotherapy and irradiation might have a slight advantage with respect to 1-year survival.[20] Complete resolution of CNS-MS following chemotherapy or radiation was reported in 24 of 125 reviewed cases by Olar et al., with overall survival after CNS-MS diagnosis found to be a few days to 114 months in 94 patients with available data.[8]

The effect of MS on prognosis is unclear.[21] In an AML registry of 240 pediatric patients, Kobayashi et al. found that the complete remission rate of patients with extramedullary manifestation of leukemia (EML) was lower than for other patients and that patients with CNS-MS who had a WBC $>100 \times 10^9$/L had lower event fee survival (23.8%) than those with no CNS-MS and/or WBC $<100 \times 10^9$/L (62.4%), suggesting that the combination of both is a risk factor for relapse.[22] In the NOPHO registry, the presence of EML was significantly associated with higher risk of death during induction therapy than non-EML patients (8% vs. 1%, $p = 0.002$), with four of the six patients (including two with CNS involvement at diagnosis) dying as a result of cerebral bleeding or infarction. EML patients also had a significantly lower 5-year overall survival (OS) of 64% compared with non-EML patients (73%) and the former.[9] Conversely, the 2012 CCG trials showed that overall survival and event-free survival (EFS) were significantly higher in orbital MS and CNS MS patients compared with non-CNS MS and non-MS patients.[10] There was also no significant difference in the bone marrow or isolated CNS relapse rate between the four groups of patients. Interestingly, analysis of children with AML from two consecutive COG Phase III trials by the CCG in 2017 demonstrated that increasing degrees of CNS involvement (i.e., CNS3 where there are >5 WBCs with blasts in cytospin or presence of chloroma) despite receiving intensified intrathecal therapy) is significantly associated with worse overall survival and disease-free survival.[23]

A multicenter French trial, conducted between 2005 and 2011, which analyzed the outcomes of children with AML and CNS involvement (CNS +) treated with the ELAM02 protocol.[17] Treatment involved induction chemotherapy with cytarabine and mitoxantrone, followed by first consolidation with high-dose cytarabine and amsacrine and then either a bone marrow transplant or two additional courses of chemotherapy. They found no significant difference in the OS between patients with CNS + (76%, 95% CI 63–84%) and without (71%, 95% CI 66–75%). Similarly, the EFS rates were also not significantly different between the CNS + (57%, 95% CI 44–67%) and CNS− group (52%, 95% CI 46–57%). There was no difference between the clinical remission rates or the percentage of patients who underwent bone marrow transplant after clinical remission between the two arms. Patients with CNS involvement had a significantly higher incidence of combined bone marrow and CNS relapse (26% vs. 10%); however, the CNS+ group had a lower rate of relapse after bone marrow transplant (5%) vs. the CNS− group (27%).

Conclusion

CNS infiltration by immature myeloid cells or myeloblasts is quite rare and can sometimes precede the diagnosis of a systemic hematologic malignancy. Diagnosis rests on a combination of IHC and histopathology of biopsied tissue. Surgical resection is controversial, especially given the efficacy of chemotherapy and radiation, and prognosis remains unclear. As with all uncommon and rare clinical entities, further investigation is warranted to determine prognosis and optimal management of CNS MSs.

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Conflict of Interest

All authors attest that there is no conflict of interest and have nothing to disclose in the submission of this paper.

Statement of Authorship

Conception or design of the work: AG, RH; Data collection: AG, KDL, AA, AR, RH; Data analysis and interpretation: KDL, RK, RH; Drafting the article: AG; Critical revision of the article: RH; Final approval of the version to be published: AG, AA, RH.

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