A Man in His 40s With Headache, Lethargy, and Altered Mental Status

Kathleen E. McKee, MD; Mark R. Etherton, MD, PhD; Scott B. Lovitch, MD, PhD; Anoopum S. Gupta, MD, PhD; Douglas S. Micalizzi, MD, PhD; Travis Tierney, MD, PhD; Martha Wadleigh, MD; Henrikas Vaitkevicus, MD

Report of a Case

A right-handed man in his 40s with no significant medical history presented with 1 month of fatigue, confusion, and headache. He initially had increased sleep requirements accompanied by poor work performance that progressed to obtundation. Associated with these symptoms, he reported several weeks of night sweats and a 10-lb unintentional weight loss. He denied any history of recent trauma or head injury. Findings from the general examination revealed left-sided cervical adenopathy and splenomegaly. Findings from the neurologic examination demonstrated markedly diminished arousal but normal cranial nerve function, motor strength, and reflexes.

Laboratory and Imaging Studies

Results from laboratory analyses were notable for a complete white blood cell count of 17,000/μL (19% neutrophils and 31% blast cells), a platelet count of 76,000/μL, and a hemoglobin level of 16.6 g/dL. Imaging studies revealed a large mixed-attenuation subdural collection in the right frontal region with prominent mass effect. The patient underwent an emergency neurosurgical procedure. The differential diagnosis, pathologic findings, and diagnosis are discussed.

Clinical Discussion (Dr McKee)

The differential diagnosis for a subacute encephalopathy is exceedingly broad. Radiographic findings and absence of seizures, however, allow for the diagnostic algorithm to be focused on mass effect from the subdural lesion. Computed tomography of the head without contrast revealed a substantial subdural collection causing midline shift with subfalcine and possible uncal herniation. In this case, the differential diagnosis for a subdural collection included hematoma, infectious processes (eg, central nervous system [CNS] abscess and/or empyema, meningitis, and tuberculosis), sarcoidosis, dural-based neoplasms (eg, meningiomas), and extramedul- lary involvement from systemic malignant neoplasms.
Subdural hematomas (SDHs) are a common cause of subdural fluid collections. The heterogeneous appearance of the subdural collection on computed tomography—with a hyperdense strip layering atop a more hypodense region—is commonly seen with acute-on-chronic SDHs. Acute SDHs are usually the result of head trauma; a sudden and severe angular shearing force results in rupture of the parasagittal or sylvian bridging veins that drain into dural venous sinuses. Chronic SDH has a different clinical presentation and typically occurs in patients who are older than 50 years because cerebral atrophy predisposes these patients to widening of the subdural space and exposure of the bridging veins; 20% to 30% of patients have no history of trauma. Acute-on-chronic SDHs represent multiple episodes of subdural hemorrhage, which can be seen in patients with coagulopathies or those who are taking therapeutic anticoagulation medications. Spontaneous cerebrospinal fluid leaks or intracranial hypotension can also produce SDHs; however, this finding is typically associated with bilateral SDHs, dural venous sinus distention, and low-lying cerebellar tonsils. The unilateral nature of this patient’s lesion and absence of these other imaging findings make cerebrospinal fluid leak and/or intracranial hypotension an unlikely etiology. The lack of hypointensity on gradient-echo sequences suggests no evidence of acute hemorrhage. Moreover, the avid enhancement shown on postcontrast sequences is typically not seen with SDH.

Infectious etiologies can also produce subdural collections. Subdural empyemas are rare causes of localized intracranial infections (15%-20%). Commonly reported symptoms of subdural empyemas include fever, headache, and vomiting. The most common sources are neurosurgical procedures, sinusitis, and otogenic sources. The patient’s recent treatment for otitis and current pain in the left ear with left-sided mastoid tenderness are indicative of infection with intracranial spread. However, the contralateral location of the lesion, month-long time course of the symptoms, and lack of fever or meningeal signs are not consistent with a bacterial subdural infection.

Atypical infectious etiologies, such as mycobacterial infections causing a tuberculous meningitis or tuberculoma, should also be considered. Tuberculous meningitis most commonly presents with basal meningeal inflammation (which this patient lacks) and/or parenchymal granuloma formation. Caseating tuberculomas may present, similar to this patient’s lesion, with T2 hyperintensity and homogeneous enhancement. Involvement of the subdural space, however, would be unusual, and aside from weight loss, the patient lacks systemic signs and tuberculosis risk factors.

Dural-based neoplasms should be considered in the differential diagnosis of any heterogeneous extra-axial mass. Both neoplastic and nonneoplastic dural-based masses occur, including primary glial, mesenchymal, and secondary neoplasms; hematopoietic neoplasms, such as Hodgkin disease and plasmacytomas; inflammatory and/or autoimmune disorder (eg, sarcoidosis); and tubercular granulomas. Meningiomas are the most common extra-axial tumors of the CNS. They are uncommon
before 40 years of age and occur more often in women (2:1). On magnetic resonance images, meningiomas are commonly homo-
geneous and well circumscribed, with postcontrast sequences showing a dural tail in 60% to 72% of cases.6 Neurosarcoidosis can also cause extra-axial lesions in the CNS; however, isolated neurosarcoidosis without systemic involvement is exceedingly rare (<1% of cases). More commonly, neurosarcoidosis affects the cranial nerves and presents with evidence of multiple cranial neuropathies. Imaging can show focal or diffuse leptomeningeal enhancement (either nodular or smooth) and/or pachymeningeal thickening.

Although uncommon, an intracranial collection of malignant hematologic cells is a distinct possibility in this case because of the new thrombocytopenia and prominent blast cells. The white blood cell differential with 31% blast cells is diagnostic for acute leukemia. The patient’s night sweats, unintentional weight loss, and spleno-

megaly further support a diagnosis of malignant neoplasm. The imaging findings are consistent with a focal collection of malignant cells; gradient-echo imaging sequences should appear isointense, and on postcontrast sequences, the collection will usually enhance. The mixed-density appearance on computed tomography is potentially secondary to varying densities of rapidly proliferating malignant cells. Extramedullary tumor involvement is rare and more often seen in cases of acute myelogenous leukemia, where it can occur in any part of the body but is most commonly located in the soft tissues, bone, peritoneum, and lymph nodes.7 In rare cases, acute lymphoblastic leukemia (ALL) may present with focal intracranial involvement.8 Thus, the most likely etiology of the patient’s subdural lesion is a collection of malignant cells secondary to a yet-undiagnosed hematologic malignant neoplasm.

Pathologic Discussion (Dr Lovitch)

Given the diminished arousal and degree of mass effect resulting in radiographic uncal herniation, the patient was taken for emergency decompression. On opening the dura, there was no evidence of acute intraparenchymal bleeding into the subdural space but rather a dense opaque membrane that was adherent to the pial surface. A small specimen was sent for frozen section and returned with findings of monotonous small round cells that were consistent with a malignant hematopoietic process. Given the tenacity of the mass to the brain and the likely diagnosis, the craniectomy was extended widely and the skin was closed without bone flap placement.

Pathologic review of tissue from the subdural lesion revealed a monotonous population of intermediate-sized mononuclear cells with round to slightly irregular nuclear contours, dispersed chromatin, frequent prominent nucleoli, and scant cytoplasm, consistent with blast cells (Figure 2A and B). Results from immunohistochemical analysis showed the blast cells to be positive for CD19, CD79a, and terminal deoxynucleotidyl transferase, with subset expression of CD20, but negative for CD3 and myeloperoxidase, consistent with lymphoblasts of B-cell lineage (Figure 2C-H).

Flow cytometry was performed using peripheral blood and revealed findings of blast cells that were positive for CD34, terminal deoxynucleotidyl transferase, CD19, CD20 (variable), and surface CD22, but negative for CD10 as well as T cell and myeloid markers.

Results from flow cytometry of the dural lesion and bone marrow were similar to those in the peripheral blood. A bone marrow biopsy revealed findings of a hypercellular bone marrow with 84%
blast cells and an immunophenotype identical to that seen in the dural lesion. In addition, results from BCR-ABL testing by reverse-transcriptase polymerase chain reaction did not find evidence of a chimeric BCR-ABL transcript.

Based on the pathologic features of the right frontal mass and the results of a bone marrow biopsy and subsequent flow cytometric analysis, the patient was diagnosed with ALL with extramedullary involvement of the subdural space.

Clinical Outcome

After hemicraniectomy, the patient began receiving intravenous dexamethasone and prophylactic leviracetam. On hospital day 8, he began receiving vincristine sulfate weekly and continued receiving dexamethasone to allow time for healing after the hemicraniectomy without inducing significant cytopenias. On hospital day 22, he began receiving induction chemotherapy with cyclophosphamide and daunorubicin citrate and continued receiving dexamethasone and vincristine with filgrastim support. The results of a bone marrow biopsy and aspirate performed on day 29 demonstrated persistent disease. The patient received another month of therapy; however, his response was transient and the patient ultimately died of complications from his underlying persistent malignant neoplasm.

Conclusions

In this case, a focal extramedullary subdural collection of leukemic cells was the presenting symptom of ALL. Although leukemic CNS complications are common, focal intracranial involvement is rare and, when reported, is almost always associated with acute myelogenous leukemia.\(^7,8\)

Leukemias are neoplasms that arise from the hematopoetic cells of the bone marrow and usually spread first to the peripheral blood but can also involve extramedullary sites. Leukemia that presents initially outside the bone marrow and mimics a solid tumor is rare but well documented.\(^9\) In acute myelogenous leukemia, extramedullary collections of leukemic cells may occur in the bone, perios teum, soft tissue, lymph nodes, skin, and rarely, the CNS. By World Health Organization classification, these extra-axial collections are labeled myeloid sarcomas,\(^7\) but many synonyms exist (eg, granulocytic sarcoma, chloroma, myeloblastoma, chloromyeloma, chloromyo sarcoma, granulocytic leukosarcoma, and myelosarcoma). Relevant to our patient, in acute lymphoblastic leukemia, leukemic involvement of the tissue is conventionally distinguished from lymphoma by establishing the presence of 20% or more blast cells in the bone marrow.\(^9\) Central nervous system involvement in ALL is most commonly meningeal—usually including diffus e dural and/or leptomeningeal infiltration by leukemic cells. This leukemic meningitis, or meningeal leukemia, is diagnosed by the detection of lymphoblasts in the cerebrospinal fluid or by neuroimaging.\(^8,10\) It is rare to develop a focal intracranial collection of extra-axial acute lymphoblastic leukemic cells.

Approximately 1 of 400 to 1 of 600 patients with ALL will develop a focal intracranial neoplasm\(^10\); however, most of these masses are found to be secondary tumors, most often glial neoplasms. These secondary tumors are usually found in patients who received craniospinal irradiation to prevent a CNS relapse of their leukemia.\(^11\) To our knowledge, there have been only 8 biopsy-proven case reports of intracranial mass lesions in patients with ALL that were caused by the original leukemia.\(^8,12-18\) These case reports refer to focal intracranial collections of ALL cells by a variety of terms, including myeloid sarcomas, granulocytic sarcomas, and chloromas. These terms are inaccurate and should be reserved for focal collections of leukemic cells of myeloid origin that express the enzyme myeloperoxidase.\(^8\) There is currently no agreed-on term for extramedullary collections of acute lymphoblastic leukemic cells. The term lymphoid sarcoma could be considered an accurate description, similar to the acute myelogenous leukemia terminology.

To our knowledge, there are no guidelines for treating myeloid or lymphoid sarcomas, but in general, operative intervention is necessary if the mass is causing life-threatening neurologic deficits, as in our patient. A review\(^19\) of 90 cases of isolated granulocytic sarcoma showed that in cases of intracranial involvement, surgical resection and/or irradiation of the tumor, although effective for local control, does not influence survival. Ultimately, systemic treatment of the underlying leukemia is the mainstay of care.

This case of an extramedullary subdural collection of lymphocytic leukemic cells, or lymphoid sarcoma, as the presenting manifestation of ALL, while rare, exemplifies the diagnostic considerations for a mixed-attenuation subdural collection in an individual with laboratory test results that indicate acute leukemia.


