



Clinical Reasoning: A 69-year-old man with leukocytosis and hemorrhagic brain lesions

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SECTION 1

A 69-year-old man was admitted to our hospital with left upper quadrant pain, splenomegaly, acute renal failure, hyperuricemia, thrombocytopenia (platelet count $32,000/\text{mm}^3$), and leukocytosis (leukocyte count $88,000/\text{mm}^3$). His medical history was significant for prior diagnosis of myelodysplastic syndrome (MDS) by bone marrow biopsy at an outside institution treated with the hypomethylating chemotherapeutic agent decitabine, atrial fibrillation, cardiomyopathy, and complete pacemaker dependence. Neurologic examination upon admission was normal. The initial diagnostic considerations were tumor lysis syndrome from decitabine treatment vs transformation of MDS to acute myeloid leukemia (AML).

Treatment with hydroxyurea and leukapheresis was initiated to reduce the leukocyte count, which reached a peak of $104,000/\text{mm}^3$ during hospitalization. Three days after admission, the patient developed dysarthria and double vision, which prompted neurologic consultation.

The neurologic examination was remarkable for esotropia OS, impaired abduction OS, impaired adduction OD, and moderate dysarthria without aphasia. Mental status, visual acuity, sensation, facial and limb motor function, reflexes, and coordination were normal.

Questions for consideration:

1. What is the most likely localization based on the examination findings?
2. What neurologic diagnostic testing should be considered at this point?

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SECTION 2

Manifest medial deviation of the left eye with impaired abduction suggests involvement of the left abducens nucleus (pons), nerve (pons, subarachnoid space, or cavernous sinus), or the lateral rectus muscle (orbit). Impaired adduction of the right eye suggests partial involvement of the right oculomotor nerve (midbrain), horizontal gaze center (paramedian pontine reticular formation adjacent to the abducens nucleus), medial longitudinal fasciculus (ponto-mesencephalon), or medial rectus muscle. Dysarthria in combination with ocular motility disturbance either suggests involvement of the corticobulbar tracts (brainstem) or a multifocal process.

A noncontrast head CT revealed multiple juxtacortical hemorrhagic lesions within the cerebral hemispheres, pons, and superior cerebellum. Several of the

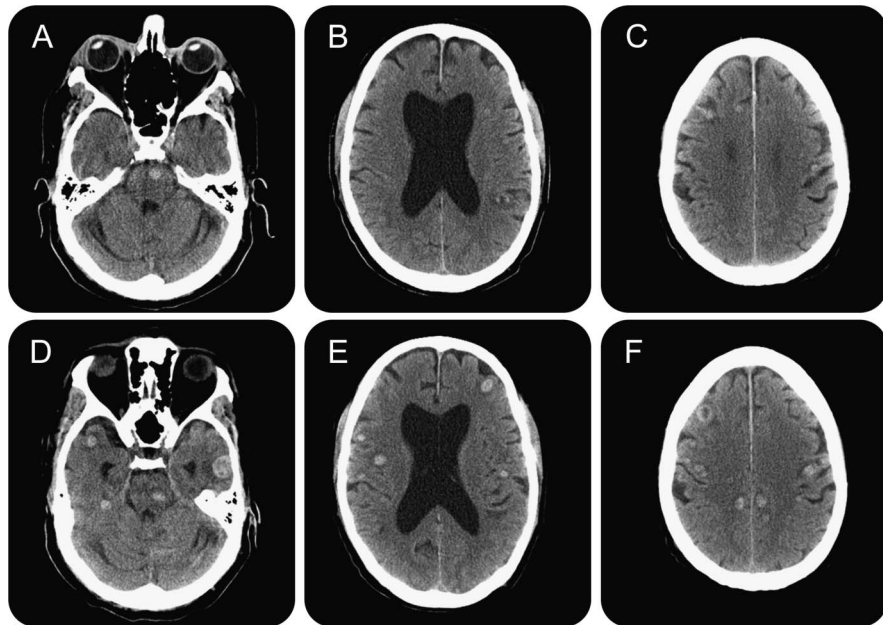
lesions demonstrated vasogenic edema without mass effect (figure 1, A–C). Brain MRI could not be safely performed due to complete pacemaker dependence. Transesophageal echocardiogram was negative for vegetations, masses, thrombi, or shunt. The working diagnosis was multifocal leukostatic infarction (ischemia secondary to vascular stasis) with hemorrhagic transformation due to leukocyte count of $104,000/\text{mm}^3$ and platelet count of $33,000/\text{mm}^3$.

Questions for consideration:

1. What is the differential diagnosis for hemorrhagic brain lesions in an immunocompromised patient with vascular risk factors?
2. What additional diagnostic studies may be of value at this juncture for the underlying systemic disease process and for the neurologic process?

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Figure 1 Initial and follow-up noncontrast head CTs



Initial head CT without contrast (A–C) demonstrates rounded hemorrhagic hyperdense lesions within bilateral cerebral hemispheres, pons, and superior cerebellum with minimal vasogenic edema. Five days later, repeat head CT without contrast (D–F) demonstrates a significant interval increase in the size and number of rounded hyperdense lesions throughout the cerebral and cerebellar hemispheres, as well as in the brainstem. Associated vasogenic edema is also mildly increased around several of the lesions, especially in the left temporal lobe and in the pons. (A–C = hospital day 4; D–F = hospital day 9.)

SECTION 3

The differential diagnostic considerations for hemorrhagic brain lesions in an immunocompromised patient with vascular risk factors include hemorrhagic infarction (cardioembolism, arterial or venous thromboembolism, vasculitis, hypoperfusion), cerebral abscess (opportunistic bacterial, fungal, or parasitic pathogens), disseminated intravascular coagulation, thrombocytopenia, cerebral amyloid angiopathy, primary or metastatic malignancy, or sympathomimetic associated hemorrhage.

Bone marrow biopsy revealed chronic myelomonocytic leukemia. Cytogenetic studies were normal. Although CD34 showed increased blasts, no increased blasts were noted on flow cytometry. The histopathologic findings were consistent with chronic myelogenous leukemia (CML) and not consistent with the outside diagnosis of MDS. There was no evidence for transformation to acute leukemia.

Lumbar puncture revealed opening pressure of 23 cm of water, 12 leukocytes (with 89% neutrophils/segs, 7% lymphocytes, and 4% monocytes), 21 erythrocytes,

glucose 90 mg/dL, and protein 26 mg/dL. Cytology was negative for malignancy. Flow cytometry could not be performed due to insufficient numbers of cells. Fungal, bacterial, mycobacterial, and viral cultures and PCRs were negative.

In addition to treatment with hydroxyurea and leukapheresis to lower the white blood cell count (i.e., cytoreduction), dexamethasone 4 mg q 6 hours was initiated to reduce vasogenic edema. Despite successful cytoreduction, neurologic deterioration occurred 5 days later with confusion, somnolence, worsening dysarthria, left facial droop, and left arm ataxia.

Questions for consideration:

1. What should be the immediate next course of action considering the progressive neurologic deterioration?
2. Given the atypical course for leukostatic infarction and the negative infectious panel, what additional diagnostic test should be performed to clarify the etiology of the intracranial lesions?

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SECTION 4

Repeat head CT revealed interval increase in the size and number of rounded hyperdense lesions throughout the cerebrum, cerebellum, and brainstem, bilaterally (figure 1, D–F). Vasogenic edema had also increased around several of the lesions with necrotic change.

The progression of hemorrhagic brain lesions despite cytoreduction suggested against leukostatic infarction with hemorrhagic transformation. Opportunistic infection or leukemic metastases were more strongly considered. The patient remained afebrile and no serologic or CSF evidence of infection became apparent. Biopsy of a superficial right frontal brain lesion revealed malignant perivascular infiltrate and transformation from chronic myelomonocytic leukemia to acute myelomonocytic leukemia (figure 2). Given the poor prognosis of diffuse CNS leukemic metastases, the patient and his family desired palliative care and the patient died 1 week later.

DISCUSSION Hyperleukocytosis is commonly defined as a leukocyte count of $>100 \times 10^9/L$ and occurs in 10%–20% of patients with AML and 10%–30% of patients with acute lymphoblastic leukemia. Patients with hyperleukocytosis are at high risk of early death due to intracranial hemorrhage and respiratory failure (i.e., symptomatic hyperleukocytosis). Leukostasis is characterized by high levels of leukemic blast cells and the diagnosis is generally made based on the presence of hyperleukocytosis and symptoms attributable to tissue hypoxia as the risk of biopsy often precludes a pathologic diagnosis. It is considered a medical emergency often seen in patients with AML or CML with high circulating blasts.¹

The underlying pathophysiology of symptomatic hyperleukocytosis is due to the presence of leukemic thrombi or aggregates in critical end organ vascular beds causing oligemia and symptoms of decreased tissue perfusion. The clinical manifestations of leukostasis are

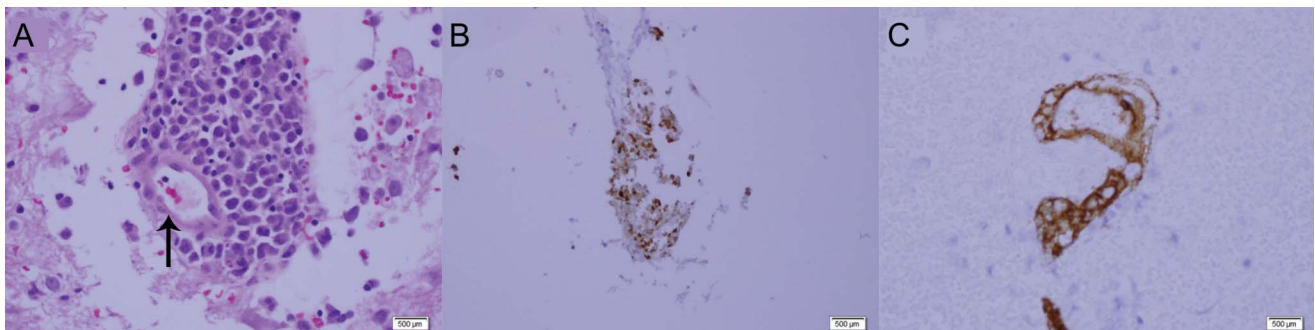
organ-dependent. Dyspnea, chest pain, hypoxemia, and diffuse interstitial or alveolar infiltrates on chest radiographs are usually seen in pulmonary leukostasis. Neurologic manifestations include headache, confusion, stupor, coma, cranial nerve deficits, ischemic stroke, intracranial hemorrhage, and retinal hemorrhage. Fever is common and cultures are usually negative. Disseminated intravascular coagulation is also common and reported in 30%–40% of patients with AML.²

The mortality rate secondary to leukostasis is high, and the severity of leukocytosis does not correlate with mortality. Clinical deterioration can occur despite adequate cytoreduction.^{2,3} Approximately 20%–40% of patients with leukostasis die within the first week of presentation.^{3–5} Patients with respiratory distress or neurologic compromise have a poorer prognosis.^{2,4} In 1 study, the presence of both respiratory and neurologic symptoms had an early mortality rate approaching 90%.⁶

Prompt cytoreduction can be achieved with hydroxyurea, induction chemotherapy, or leukapheresis. Reduction in leukocyte count can be expected within 24–48 hours of treatment initiation. Leukapheresis remains the mainstay of treatment for symptomatic hyperleukocytosis since its introduction more than 20 years ago. Although leukapheresis can effectively reduce the leukocyte count, treatment may not change patients' overall mortality or reverse the clinical consequences of leukostasis.^{2,4} Leukapheresis may lower the risk of early death in patients with AML and hyperleukocytosis.⁵

In this case, the presence of intracranial hemorrhage in the setting of hyperleukocytosis was suggestive of leukostatic ischemic infarcts with hemorrhagic transformation, but the patient continued to deteriorate despite successful cytoreduction. Though clinical deterioration can be seen after cytoreduction, development of new neurologic symptoms prompted the search for an alternate etiology. Ultimately,

Figure 2 Salient histopathology from intracranial lesional biopsy



(A) Hematoxylin & eosin stain demonstrates a blood vessel (arrow) with perivascular malignant infiltrate. (B) Establishes the diagnosis of malignant myeloid cells with myeloperoxidase positivity. (C) Establishes the diagnosis of immature myeloid cells (i.e., acute myeloid leukemia) with CD34 positivity.

intracranial lesional biopsy confirmed a different (or perhaps additional) mechanism for the intracranial hemorrhages (i.e., transformation to acute leukemia with CNS deposits/metastases).

Although CNS involvement is not uncommon in acute leukemia, pachymeningeal and leptomeningeal deposits are more common than perivascular or parenchymal deposits as were found in our patient.⁷ Evidence suggests that leukemic cells infiltrate directly from the bones of the skull into the perivenous adventitial tissue linking the skull to the dura and arachnoid.⁷ Thus, leukemic CNS infiltration tends to follow a superficial to deep pattern of progression with the meninges being affected more often than the brain parenchyma. The hallmark clinical features of leptomeningeal infiltration are cranial neuropathies, headache, altered mental status, and radiating pain due to nerve root involvement. Treatment consists of radiation, intrathecal chemotherapy, or systemic chemotherapy with agents that produce adequate CSF drug levels such as methotrexate or cytarabine.⁸

Acute/chronic leukemias and myeloproliferative disorders are also capable of producing intraparenchymal solid masses composed of myeloid precursor cells. These solid masses are referred to as chloromas (also known as myeloid sarcomas or granulocytic sarcomas). Chloromas occur in multiple tissue types, but CNS involvement is rare.^{9,10} Hemorrhagic complications from acute leukemia occur in 20% of all cases. CNS chloromas are treated with high-dose corticosteroids and whole-brain radiation.

This case not only illustrates an unusual presentation of CNS leukemic metastasis, but also highlights the expansive differential of multifocal intracranial lesions in the immunocompromised oncologic patient. The initial diagnosis of cerebral leukostasis with hemorrhagic infarction was reconsidered following progressive neurologic deterioration despite successful cytoreduction. Lesional biopsy led to the correct diagnosis of acute myelogenous leukemia with CNS deposits/metastases. The case also illustrates the value of multidisciplinary collaboration, careful and serial examination of the patient, and the incorporation of new clinical information to arrive at the correct diagnosis.

AUTHOR CONTRIBUTIONS

Dr. Scott: study concept, acquisition and interpretation of data, writing of the manuscript, critical revision of the manuscript for intellectual

content, final approval of the manuscript. Dr. Gardner: acquisition and interpretation of data, writing of the manuscript, critical revision of the manuscript for intellectual content, final approval of the manuscript. Dr. Eidelman: study concept, final approval of the manuscript. Dr. Rivera: critical revision of the manuscript for intellectual content, final approval of the manuscript. Dr. Barrett: writing of the manuscript, critical revision of the manuscript for intellectual content, final approval of the manuscript. Dr. Menke: acquisition of pathology information/image, construction of the manuscript, final approval of the manuscript.

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