

Intracranial hematopoiesis in a patient with aids-related central nervous system lymphoma and severe pancytopenia

The case here reported reflects the difficulty in diagnosing meningeal extramedullary hematopoiesis (EMH), which clinically appeared concomitantly with primary cerebral lymphoma and occurred in a patient with HIV infection and severe pancytopenia. Pancytopenia secondary to HIV infection could be hypothesized as a predisposing factor for the ectopic development of hematopoietic tissue outside the bone marrow. Although rare, intracranial EMH should always be considered in the differential diagnosis of headache and other endocranial hypertension symptoms in patients with chronic bone marrow dysfunction

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A 36-year old woman was admitted to our hospital for cough, septic fever, decreased visual acuity in the left eye, and dysphagia. Laboratory tests revealed the presence of pancytopenia (hemoglobin, 8 g/dL; neutrophils, 900/ μ L; lymphocytes, 500/ μ L; platelets, 40,000/ μ L), with total serum protein of 12 g/dL and polyclonal hypergammaglobulinemia. Microscopic examination of peripheral blood smears did not show either blasts or erythroid/myeloid precursors. Hemoglobin electrophoresis was normal. CD4⁺ lymphocyte count was 10/ μ L and HIV-Ab seropositivity (ELISA test confirmed by Western blot) was detected, with HIV-RNA viremia of 37000 copies/mL. In addition, blood cultures produced the growth of acid-alcohol resistant mycobacteria. Conventional chest radiography and computed tomography (CT) scan of brain, thorax and abdomen were negative. Esophagogastroscopy and biopsy revealed severe mucosal candidiasis. Standard ophthalmologic exam and indirect ophthalmoscopy of the left eye showed signs of cytomegalovirus (CMV) chorioretinitis, which was confirmed by detection of positive CMV antigenemia.

A final diagnosis of Acquired Immune Deficiency Syndrome (AIDS), category C, based on the Centers for Disease Control (CDC) categorization, was made.

The patient received antibiotic, antimycotic (fluconazole), anti-tubercular (rifabutin, ethambutol), anti-CMV (ganciclovir), and antiretroviral (emtricitabine/tenofovir, fosamprenavir, enfuvirtide) therapy without any clinical improvement. Pancytopenia was still present, with a progressive decreasing trend in platelet count (lowest value: 20,000/ μ L). Three months after AIDS diagnosis, the patient developed headache and endocranial hypertension signs with progressive deterioration of consciousness. A brain CT scan disclosed multiple bilateral cortical and subcortical solid lesions without either perifocal edema or cavitation (Figure 1 A, B). Cerebral biopsy revealed a lymphoid infiltration with an immunohistochemical phenotype of diffuse large cell B lymphoma (DLCL). Whole brain radiotherapy was started with endovenous high-dose dexamethasone (20 mg daily) administration, but symptoms rapidly progressed leading to coma. A craniotomy was finally performed. Intracranial pressure was 400 mmH₂O and the cerebrospinal fluid (CSF) count was of 20 nucleated cells per mm³. Microscopic analysis of the CSF showed varying numbers of hematopoietic cells from both erythroid and myeloid cell lines (Figure 2 A, B). No lymphoma cells were detected. Two subsequent CSF samples showed

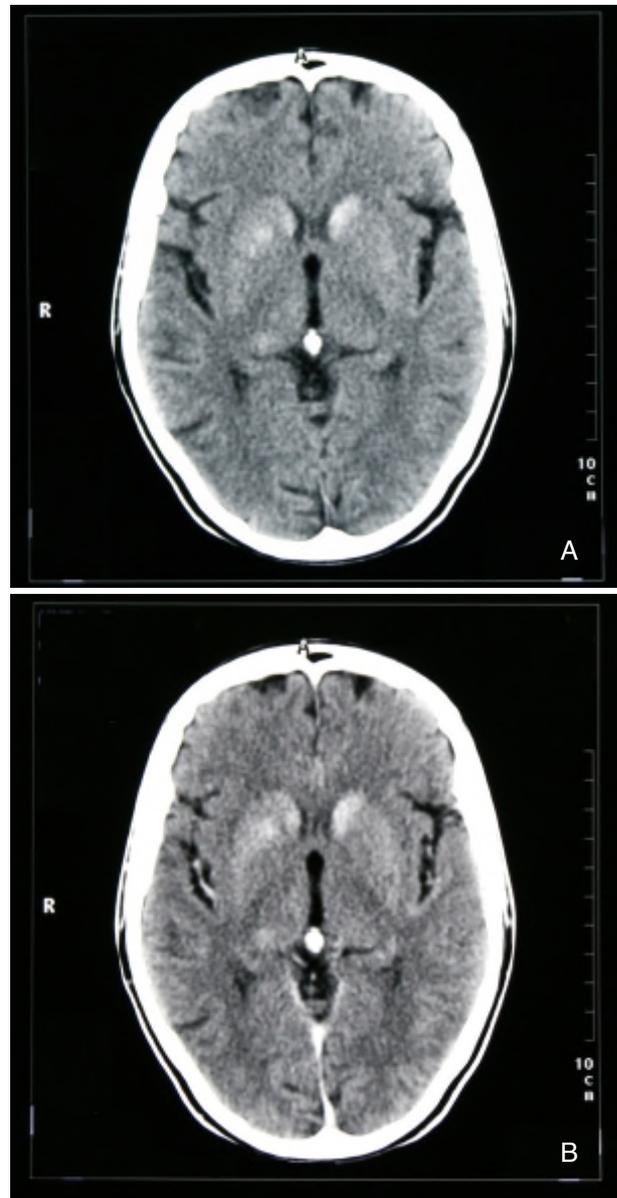


Figure 1. Cerebral CT scan. (a) Un-enhanced and (b) enhanced axial CT scan of the brain showing bilateral hyperdense soft-tissue lesions.

specular microscopic findings. Peripheral blood smears still confirmed the pancytopenia without either erythroid or myeloid precursors. Two weekly injections of intrathecal methotrexate (15 mg) were administered, but the patient died twenty days after starting treatment. An autopsy was not performed at the request of the family.

Extramedullary hematopoiesis (EMH) is a physiological compensatory mechanism for ineffectual hematopoiesis. It refers to deposits of myeloid precursors in sites other than the bone marrow. EMH can occur in several hematological conditions, namely: congenital hemolytic anemias, such as thalassemia; severe hemolytic states or ineffective erythropoietic states, such as pernicious anemia; and conditions where control of stem cell differentiation is lost, such as myelofibrosis or polycythemia vera.¹ Most often found in the liver, spleen and thoracic paraspinal regions, EMH more rarely affects other organs

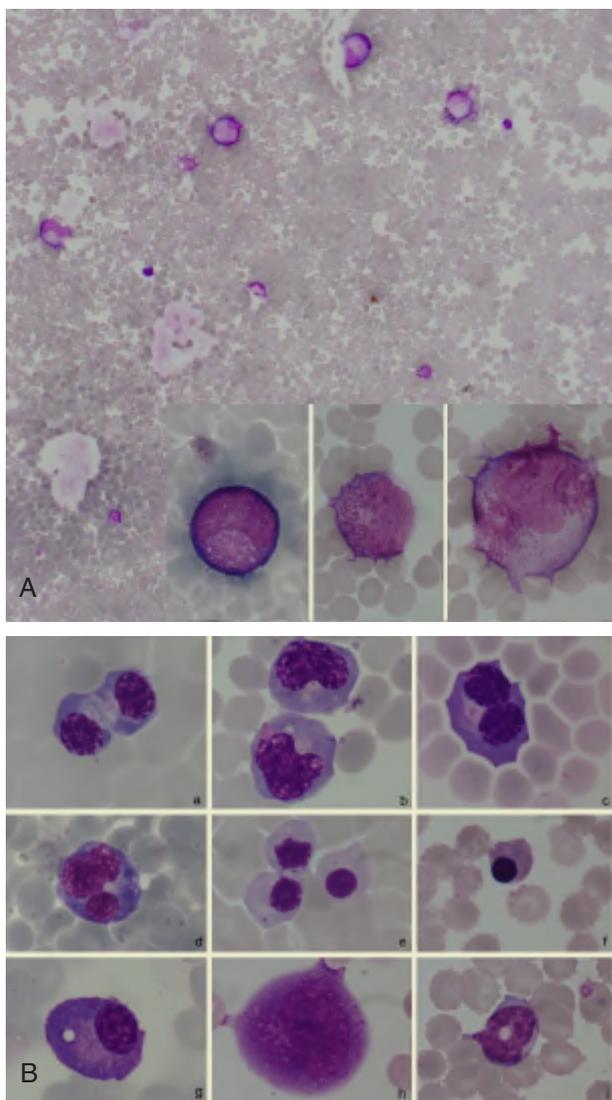


Figure 2. Cerebral spinal fluid (CSF) cytology. (A) A composite figure showing at low magnification the scant cellularity of the fluid and the haematic background (MGG stain, x100). The insets show myeloid precursors: two normal and one abnormal promyelocytes (MGG stain, x1000). (B) Precursors of hematologic cells found in the cerebrospinal fluid: a-b-c-d, basophilic eritroblasts; e-f, polychromatophilic eritroblasts; g, plasmocyte; h, unclassified cell; i, cell with a ring-shaped nucleus.

of the body.² Diagnosis of EMH can be made by tissue biopsy, but fine needle aspiration cytology can also play an important role in confirming EMH.^{3,4} Intracranial EMH is rare.⁵ The most frequently reported causes of intracranial involvement by EMH are thalassemia (50%) and myelofibrosis (31%).^{6,7} Intracranial EMH most frequently involves the cranial dura and falx, followed by the cerebral parenchyma, optic nerve sheath and the leptomeninges.^{8,9} Various speculative hypotheses such as development from embryonic rests, transformation of multipotent epidural cells, embolization from distant marrow sources, direct extension from bone marrow and migration from the vascular bed have been hypothesized. In recent studies, the role of fibrogenic cytokines, such as transforming growth factor- β (TGF- β) and basic-fibroblast growth factor (b-FGF), has been suggested.¹⁰

The present case is, to our knowledge, the first reported case of EMH occurring in a patient with AIDS.

Pancytopenia secondary to HIV infection could be hypothesized as a predisposing factor for the ectopic development of hematopoietic tissue outside the bone marrow. In patients with HIV infection, pancytopenia can result from the disease or related malignancies, immune mechanisms, drug therapies, or opportunistic infections.¹¹ HIV can cause pancytopenia, specially neutropenia, by directly or indirectly impairing hematopoiesis. Similarly, microorganisms that cause opportunistic infections, such as cytomegalovirus and mycobacterium avium complex, can infiltrate the bone marrow and cause myelosuppression. Hematologic toxicities of drug therapy targeted against HIV and opportunistic infections can further reduce blood cell formation. Although bone marrow biopsy was not performed in this case, several studies described histopathological changes in bone marrow of HIV/AIDS patients.¹² Common histopathological features, which were suggestive but non-pathognomonic, were: reticular fibrosis (58.6%), iron deposits (59.2%), severe hypoplasia (30%), vascular congestion and mucoid degeneration of fat (18.4%).

The case here reported reflects the difficulty in diagnosing meningeal EMH, which clinically appeared concomitantly with primary cerebral lymphoma and occurred in a patient with HIV infection and severe pancytopenia. Although rare, intracranial EMH should always be considered in the differential diagnosis of headache and other endocranial hypertension symptoms in patients with chronic bone marrow dysfunction.

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