

Granulocytic sarcoma: an unusual complication of acute promyelocytic leukemia causing cerebellar hemorrhage

Case report

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✓ Granulocytic sarcomas are rare tumors that occur primarily in patients with acute myelogenous leukemia or other myeloproliferative disorders, are seldom seen in patients with acute promyelocytic leukemia (APL), and have never been reported to occur in the cerebellum. The authors describe the case of a patient with APL who harbored a hemorrhagic granulocytic sarcoma in the cerebellum. This 39-year-old woman presented with cerebellar ataxia. Magnetic resonance images revealed an intraaxial tumor in the cerebellum. Bone marrow samples showing infiltration by leukemic blast cells and data from hematological tests led to a diagnosis of APL. The patient was treated with chemotherapy and surgery. She had no response to chemotherapy and died of progressive intratumoral hemorrhage. Results of histopathological studies and immunohistochemical staining of the cerebellar tumor confirmed a granulocytic sarcoma. Flow cytometry showed that the blast cells were positive for leukocyte common antigen, CD13, and CD33 markers. Bone marrow cytogenetics revealed that the patient had a 46,XX karyotype. Although no cytogenetic abnormality was present, fluorescence in situ hybridization detected a chimeric fusion of *PML* and *RARA*.

This is the first report to document a granulocytic sarcoma in the cerebellum as the primary presentation in a patient with APL and abnormal coagulation. As predicted by the unusual clinical manifestations and radiological findings, the patient's survival was short. Although central nervous system complications in patients with APL are rare, the data in this case highlight the need for individualized treatment when such conditions occur.

KEY WORDS • acute promyelocytic leukemia • granulocytic sarcoma • cerebellum

GRANULOCYTIC sarcoma is a rare tumor composed of immature granulocytes. The disease generally has a poor outcome, and the survival time in patients is short.² Only 3% of granulocytic tumor cases occur together with myelogenous leukemia;¹⁴ however, the true incidence of these sarcomas may be different. The majority of these neoplasms are discovered at autopsy, although in one study, only 52% of myelogenous leukemia cases included post-mortem examinations.¹⁰

Acute promyelocytic leukemia is characterized by the proliferation of abnormal promyelocytes and is classified as type M3 in the French-American-British leukemia system.¹ Clinically, the high incidence of disseminated intravascular coagulation affects prognosis.¹⁸ A translocation between the long arms of chromosomes 15 and 17 is a cytogenetic feature of APL,¹² and the fusion between *RARA* and *PML* has therapeutic significance.¹⁶

Although they may be found anywhere in the body, granulocytic sarcomas most frequently occur near bone and are often present in perineural and epidural structures.^{13,21} To

our knowledge, this report is the first on a patient with APL, coagulation abnormalities, and hemorrhagic granulocytic sarcoma in the CNS.

Case Report

History and Examination. This 39-year-old woman presented with a 2-week history of cerebellar ataxia. Results of a gross physical examination revealed a spontaneous ecchymosis on her right thigh. Cranial MR images showed a 30-mm mass in the left cerebellar hemisphere together with perifocal edema. The lesion was isointense on T₁-weighted MR images, appeared hyperintense compared with normal brain tissue on T₂-weighted MR images, and had peripheral rim enhancement after the administration of Gd-diethylenetriaminepentaacetic acid (Fig. 1A and B). A complete blood count revealed leukocytosis ($47.6 \times 10^9/L$), consisting of 97% myeloblasts with Auer bodies, and a low platelet count ($14 \times 10^9/L$). Coagulation studies indicated low fibrinogen (0.124 g/dl) and high fibrin degradation products (15.2 μg/ml). Photomicrographs of May-Giemsa-stained bone marrow samples (Fig. 2) revealed the proliferation of abnormal promyelocytes. Cytogenetic studies revealed that the patient had a 46,XX karyotype, but fluorescence in situ hybridiza-

Abbreviations used in this paper: APL = acute promyelocytic leukemia; ATRA = all-trans retinoic acid; CNS = central nervous system; MR = magnetic resonance.

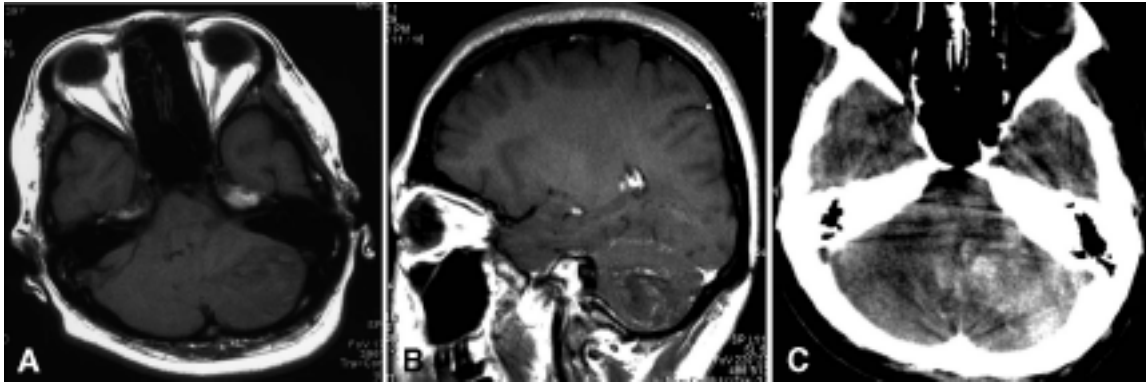


FIG. 1. A: Axial MR image (TR 500 msec, TE 9 msec) showing an intraaxial tumor solely in the left cerebellar hemisphere. B: Sagittal contrast-enhanced spin echo T₁-weighted MR image (TR 470 msec, TE 20 msec) revealing a thin enhancing rim around the mass. C: Axial computed tomography scan revealing intratumoral hemorrhage.

tion detected a chimeric fusion between *PML* and *RARA* (Fig. 3). Based on the results of these radiological and hematological tests, we diagnosed a lymphomatoid lesion and APL.

Treatment and Posttreatment Course. We initially treated the patient with chemotherapy: idarubicin, 10 mg/m²/day; and arabinosylcytosine, 1000 mg/m²/day. Three hours after admission, she experienced a deep coma due to a growing cerebellar hemorrhage (Fig. 1C). We performed posterior fossa decompression. The patient had progressive abnormal coagulation and died 4 days after surgery. Results of histological examination and immunohistochemical testing for myeloblastic markers of the hemorrhagic brain tissue confirmed our diagnosis of granulocytic sarcoma of the cerebellum (Fig. 4). Flow cytometry indicated that the blast cells were positive for leukocyte common antigen, CD13, and CD33.

Discussion

Acute promyelocytic leukemia is the most curable subtype of acute myeloid leukemia, which is a hematological disorder characterized by an abnormal proliferation of immature myeloid cells.¹⁸ Note, however, that the disease cannot always be cured, usually because of coagulopathy or relapse. Furthermore, granulocytic sarcoma is rarely the cause.

Granulocytic sarcoma is most frequently associated with acute myelogenous leukemia, particularly with subtypes M2, but has also been associated with other myeloproliferative disease such as chronic myelogenous leukemia, polycythemia vera, hypereosinophilia, and myeloid metaplasia.¹⁵ Although granulocytic sarcoma can affect any organ and has many modes of presentation, its occurrence is rare in promyelocytic leukemia and even rarer as a primary presentation. The patient in the present case was unique: an adult patient with APL and abnormal coagulation presenting with hemorrhagic granulocytic sarcoma in the cerebellum, to our knowledge, has never been reported previously in the literature. Additionally, this patient had a normal karyotype but a *PML/RARA* chimeric gene fusion.

We used immunohistochemistry to validate our diagnosis of granulocytic sarcoma. Because of their similar histopathologies in biopsy specimens, granulocytic sarcomas

may be mistaken for large-cell lymphomas.²⁰ Immunohistochemical tests with chloroacetate esterase stain, antilysozyme immunoperoxidase reaction, and antimyeloblast monoclonal antibodies confirmed the granulocytic nature of the tissue.¹⁵

In patients with hemorrhagic abnormalities treated with antileukemia therapy, cerebrovascular complications have been the major cause of low survival rates.⁸ In a recent series, 10.5% of patients who received antileukemia drugs suffered cerebral hemorrhages that were identified during intervention.³ In a large series of 194 adult patients with acute nonlymphoblastic leukemia, 30 (15.5%) had intracranial hemorrhages (including four patients with cerebellar hemorrhage) that had been diagnosed based on either computed tomography or autopsy findings.²² In patients with APL, an initial leukocyte count greater than $4 \times 10^9/L$ and a platelet count less than $20 \times 10^9/L$ were associated with an increased risk of intracranial hemorrhage⁹ and with death within 24 hours.¹⁷ The patient in the current report presented with hyperleukocytosis ($47.6 \times 10^9/L$) and thrombocytopenia ($14 \times 10^9/L$), abnormalities that suggested possible hemorrhagic complications.

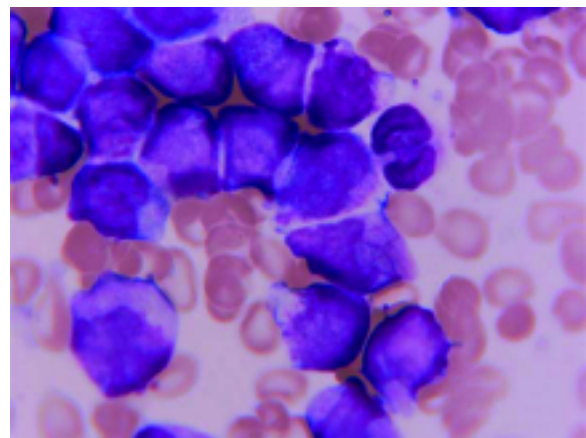


FIG. 2. Photomicrograph showing an atypical myeloblast with Auer bodies consistent with APL. May-Giemsa, original magnification $\times 250$.

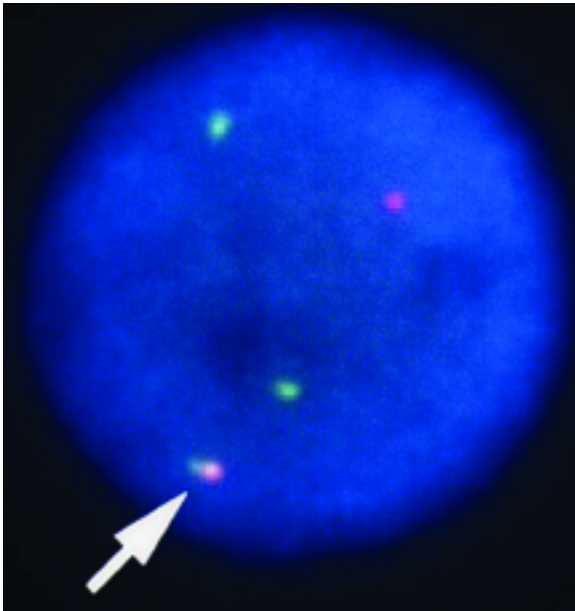


FIG. 3. Fluorescence in situ hybridization image demonstrating a *PML/RARA* chimeric gene fusion (arrow).

In a patient with APL and granulocytic sarcoma of the CNS, the decision to perform surgery for the neoplasm or to treat the APL with antileukemia drugs depends on the patient's hematological condition. Because of the thrombocytopenia and abnormal coagulation values in the patient in the present case, we chose as the initial therapy antileukemia drugs rather than tumor resection. The direct benefit or detriment of early antileukemia therapy on cerebrovascular complications is unknown. All-*trans* retinoic acid permits myeloid differentiation of the leukemic promyelocytes and is used as a first-line treatment for APL.¹⁹ Combination therapy with ATRA significantly reduces the incidence of disease relapse.¹¹ Chung and colleagues⁴ reported successful treatment for cerebral hemorrhage with an early combination of white blood cell components and ATRA followed by standard chemotherapy. However, most authors describe adverse effects of ATRA therapy in patients with APL.⁷ Current evidence suggests that because it increases the expression of adhesion molecules on leukemic promyelocytes and their ligands on endothelial cells, ATRA may facilitate the passage of malignant promyelocytes across the blood-brain barrier and predispose patients to relapse at unusual sites.⁶ Therefore, no conventional therapy was available to the high-risk patient in the present case. Treatment must be individualized for each patient based on hematological condition, clinical presentation, and tumor location.

Central nervous system complications in leukemia are an uncommon presentation, but 5 to 7% of patients with myelogenous leukemia have asymptomatic CNS involvement, as determined by positive cerebrospinal fluid cytological analysis.⁵ Nonetheless, concomitant asymptomatic CNS disease alone does not result in a poor prognosis.¹³ The patient with APL in the present case had hemorrhagic granulocytic sarcoma, which predicted a short survival. Identification of a granulocytic tumor as hemorrhagic may indicate surgical management and predict survival time.

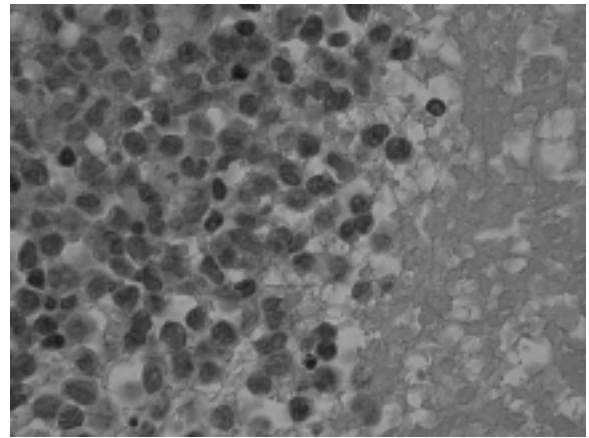


FIG. 4. Photomicrograph obtained after histological examination of the hemorrhagic brain tissue, showing infiltrating cells that were ovoid or polygonal. Nuclei were hyperchromatic with occasional prominent nucleoli. The cytoplasm was generally scanty. H & E, original magnification $\times 400$.

Conclusions

This report is the first on a granulocytic sarcoma of the cerebellum in a patient with APL. The tumor caused an intratumoral hemorrhage because of abnormal coagulation. Granulocytic sarcoma in a patient with APL and coagulation abnormalities is associated with a short survival.

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