Intracranial acute promyelocytic leukemia at presentation—A case-based discussion

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ABSTRACT

Intracranial disease is a very rare presentation at diagnosis in acute promyelocytic leukemia (APL). The risk associated with this particular presentation is not accounted for when the current risk stratification is based on peripheral counts. Extra medullary disease in general may challenge this risk stratification that commands initial induction treatment of this potentially fatal disease. Here we discuss a case presented at diagnosis with extensive intracranial base of the skull, clivus and sinus infiltration and heavily infiltrated bone marrow yet with low peripheral blood counts and no peripheral blood blasts. Such cases lack evidence of how to treat.

1. Introduction

Acute promyelocytic leukemia (APL) is a biologically and clinically distinct variant of AML. APL was classified as AML-M3 in the older French-American-British (FAB) classification system and is currently classified as acute promyelocytic leukemia with t (15; 17) (q24.1; q21.2); PML-RARA in the World Health Organization classification system [1].

APL represents a medical emergency with a high rate of early mortality, often due to hemorrhage from the characteristic coagulopathy that is associated with the diseases. It is critical to start treatment with a differentiation agent (e.g., all-trans retinoic acid) without delay as soon as the diagnosis is suspected based upon cytological criteria, and even before definitive cytogenetic or molecular confirmation of the diagnosis has been made. APL can occur at any age; it has lower frequency in elderly patients. Depending on geographic variations, APL accounts for 5–20% of AML cases; there appear to be approximately 600–800 new cases per year in the United States [2,3]. With the use of all-trans retinoic acid (ATRA) and improved survival in patients with APL, still approximately 10% to 20% of APL cases relapse. Based on the Italian GIMEMA and the Spanish PETHEMA trials, patients with APL are traditionally risk stratified according to total white blood cell (WBC) and platelet count at presentation [4]. Using these two parameters, three prognostic categories were distinguished: (1). Low risk – WBC $\leq 10,000/\mu l$ and platelets $>40,000/\mu l$; with recurrence free survival (RFS) of 98%, (2) Intermediate – WBC $\leq 10,000/\mu L$ and platelets $\leq 40,000/\mu L$ with RFS 89% and (3). High risk – WBC $>10,000/\mu L$; with RFS 70%. More recently, ATRA plus arsenic trioxide have been shown to at least be not inferior and may be superior to ATRA plus chemotherapy in the treatment of patients with low-to-intermediate-risk [5]. There is less certainty regarding the preferred approach for patients with a high WBC count at presentation. ATRA plus chemotherapy remains the recommended initial therapy for high-risk APL until more data are available regarding the early use of ATO in this small subset [6]. This risk stratification, however, does not necessarily cover the whole spectrum of APL clinical presentation and leaves out patients that may have higher risk due to other factors. Two of those additional factors presented in this case report need to be examined; (1). Extramedullary presentation especially central nervous system involvement and, (2). The disease burden as reflected by how heavy the marrow is replaced by APL blasts. CNS disease not only increases disease burden but require CNS directed therapy designed to effectively cross the blood brain barrier. Heavy marrow infiltration may also represent a higher disease burden similar to what higher peripheral count represent. Both need to be taken into account when treatment is planned and low intensity treatment may not be appropriate for these unique cases. We report here on a case that would have been stratified as low risk by virtue of peripheral counts. This patient's unique presentation could t in fact at put her at a significant additional risk because of extensive infiltration of the base of the skull and the clivus at diagnosis and possibly because of the high disease burden in the bone marrow which was completely replace by APL blasts. These two
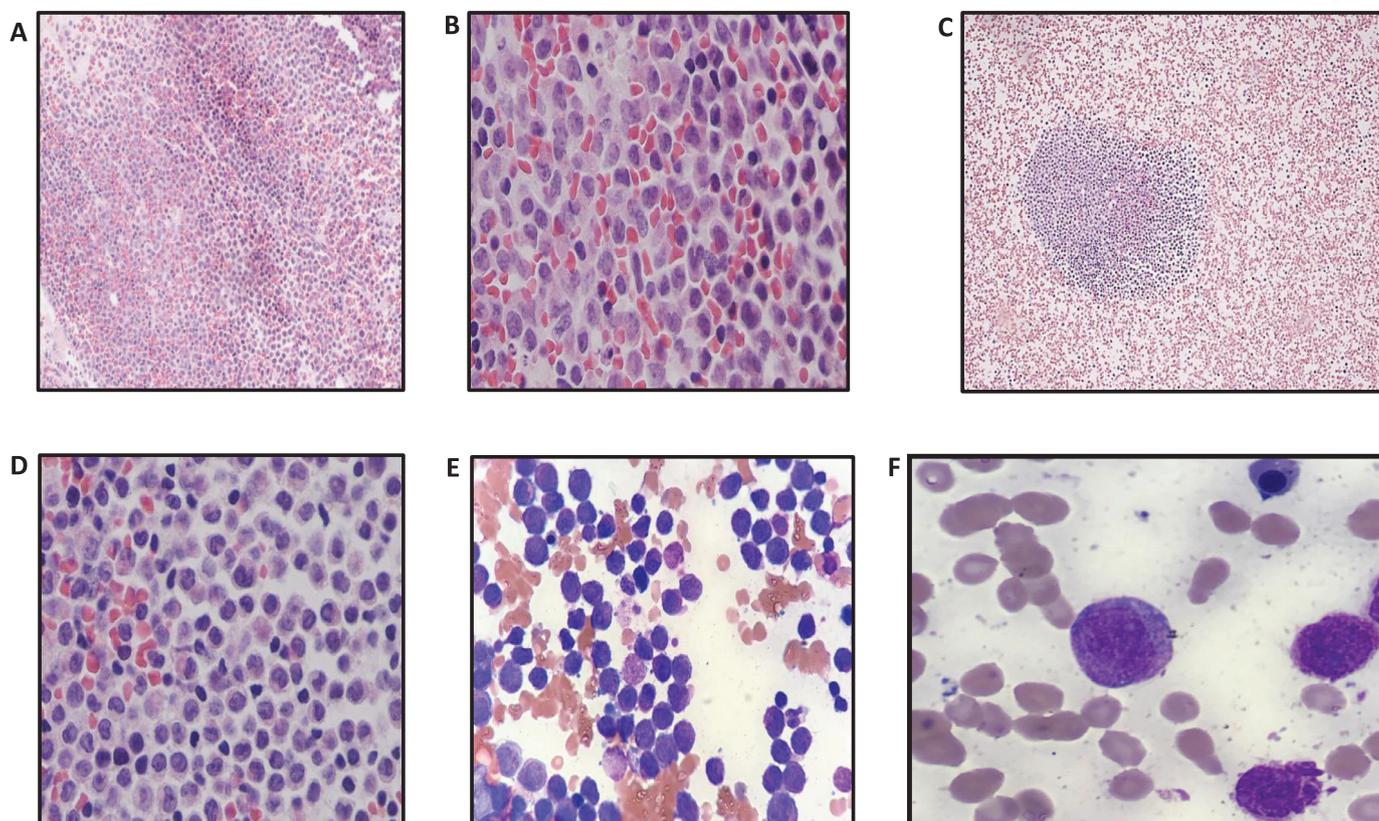
Fig. 1. Bone marrow core biopsy: (A) low power (4×) sheets of malignant promyelocytes replacing the bone marrow and (B) high power (40×) showing promyelocytes with varying size and shape, occasional kidney shaped nuclei, and dense cytoplasm with pink granules. (C) Clot: low power (4×) showing a monotonous population of myeloid cells, and (D) high power (40×) of the malignant promyelocytes with similar features as the above bone marrow core. (E) and (F) Aspirate at (100×, oil) shows the morphologic characteristics of acute promyelocyte leukemia, enlarged nuclei with nucleoli, moderate cytoplasm with dense azurophilic granules and occasional Auer Rods. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

features may reflect a higher risk disease despite the low peripheral WBCs and platelets counts.

2. Summarized case report

The patient is a 39-year-old female presented with pancytopenia, abnormal uterine bleeding, gingival bleeding and headache. Physical examination revealed ecchymosis on bilateral upper extremities and a small hematoma at previous bone marrow biopsy site with no focal neurologic deficits. A complete blood count showed pancytopenia including a white blood cell (WBC) count of $0.39 \times 10^9/L$ (N: $4.5–11.0 \times 10^9/L$), hemoglobin (Hb) level of 9.2 g/dL (N: 13.3–17.3 g/dL), and a platelet count of $41 \times 10^3/uL$ (N: $150–450 \times 10^3/uL$). LDH was mildly elevated at 399 IU/L (N: 94–250 IU/L). Coagulation studies indicated low fibrinogen (247 mg/dL, N: 250–550 mg/dL) and high D-Dimer (9806.0 D-DU ng/mL, N: <230 D-DU ng/mL). Prothrombin Time (PT) and Prothrombin Time (PTT) values were normal. The peripheral blood showed no blasts. However, upon bone marrow examination (Fig. 1) by aspirate and touch-prep showed hypercellularity with virtual replacement by promyelocytes with nucleoli, cytoplasmic granules, and occasional Auer rods. Immunophenotyping of the bone marrow by flow cytometry revealed an immunophenotype consistent with APL, positive for CD33, low intensity CD15, myeloperoxidase (MPO), CD117, CD123, and CD38 and negative for DR (Fig. 2).

Cytogenetic analysis of the bone marrow from showed translocation of chromosome 15 to chromosome 17. FISH, Dual Color Dual Fusion probe (PML-15q22 Spectrum Orange, RARA-17q21.1 Spectrum Green) sowed two fusion signals (t15; 17) (q22; q21), (Fig. 3). The patient marrow did not have any secondary cytogenetic abnormalities and no molecular mutations such as FLT3-ITD were found. Because of

persistent headache, cranial magnetic resonance images (MRI) showed extensive infiltrative lesions involving the clivus, the right maxilla, and right mandible but no intracranial bleeding or mas formation (Fig. 4). A lumbar puncture was also performed. CSF cytology reviled similar APL myeloblasts as seen in the marrow. CSF flow cytometry analysis demonstrated the same population of APL blasts as seen in the bone marrow, consistent with CSF involvement (Fig. 5A and B).

According to the currently used risk stratification, this patient will be classified as low risk disease. However the critical extramedullary site involvement and a high disease burden as reflected by virtual complete marrow replacement with APL blasts prompted a different treatment approach based on a clinical judgment of higher risk assignment. We treated her as a high risk disease with CNS directed chemotherapy induction regimen. We used daunorubicin at 90 mg/m² for 2 days and cytarabine at 100 mg/m² for 5 days. Additionally intrathecal cytarabine at 100 mg was administered twice weekly until CSF was cleared of APL blast cells. It took 8 weeks to clear her CSF. IT chemotherapy was continued for three additional months once monthly. For additional systemic treatment and on Day 14 post chemotherapy arsenic and ATRA (per German–Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia) were initiated and completed [5]. Afterwards, she was maintained on 6MP and ATRA as with high risk patients. This patient accomplished molecular remission at all involved sites. Her intracranial disease resolved completely, Fig. 4B. She has maintained remission for 8 months by the time of this report.

3. Discussion

Extramedullary intracranial involvement with APL is a rare
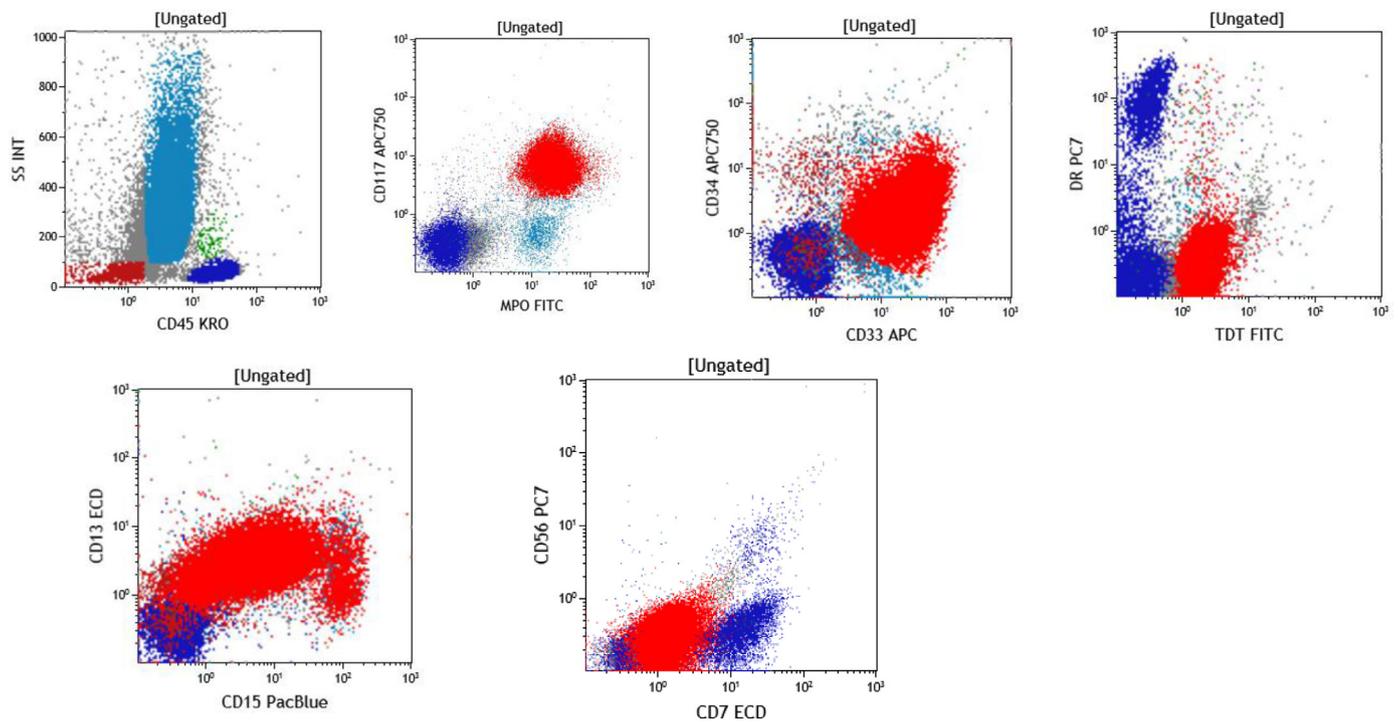
Fig. 2. Flow cytometry of the bone marrow aspirate, showing a population of MPO+, CD117 dim +, CD33+, HLA-DR and TDT -, CD15-, CD64-, CD14-, CD13 dim + and CD56- population of myeloid blasts (red), Consistent with APL. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

complication and is more often seen in relapsed disease than at presentation. Additionally, a negative peripheral blood for APL blasts is virtually unreported to date. Together with intracranial clinical and radiographical findings, the absence of APL blasts in the peripheral blood challenged early diagnosis and delayed prompt treatment in this patient. APL presentation at diagnosis with CNS involvement has only been reported rarely in both pediatric and adult population, none of these cases occurred without peripheral blood involvement [7,8]. Although rare, CNS is the most common site that is affected during extramedullary relapse with an incidence of 0.6–2.0% [7]. Even then, most cases present with peripheral blasts and hemorrhage at the time of relapse in the CNS [9,10]. Our case, presented with intracranial disease without evidence of peripheral blood involvement with APL blasts. This presentation is rare and could potentially confer a higher risk.

Despite the almost invariable presence of circulating blasts, it has been observed that leukemic cells in some cases adhere to the marrow and don't get released into the peripheral blood all that early. This might indicate intramedullary disease progression and growing burden with no detectable indicators other that the associated pancytopenia. Adhesive properties of leukemia cells are also likely responsible for the leukostatic complications of AML such as leukemic meningitis, leukemia cutis, extramedullary leukemia, formation of chloromas and possibly the lack of circulating blasts in the peripheral blood. Three receptors, VLA- (very late antigen-) 4, CXCR4, and CD44, play a critical role in normal stem cell homing and also appear to be paramount to the homing of AML cells to, or retention within, the bone marrow [11–14]. If those cell adhesion proteins are not lost, it is less likely that peripheral blood will show blast infiltrations and it will be more likely to have extramedullary homing and tissue infiltration. Our case could be only one example of these distinct pathologies. Hence, patients with these
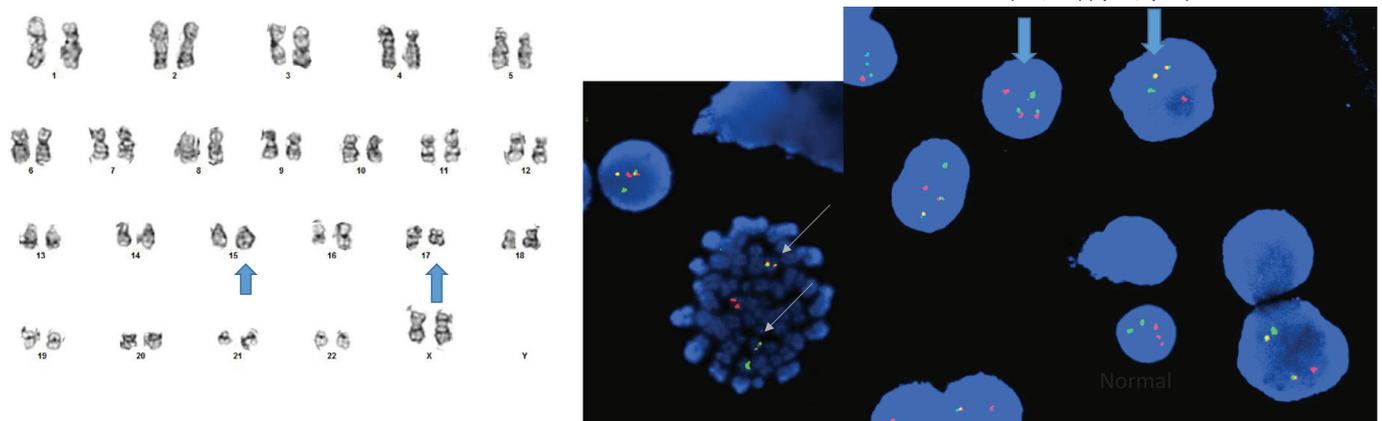
Fig. 3. Cytogenetic analysis of bone marrow from initial diagnosis. (A) Karyotype showing translocation of chromosome 15 to chromosome 17. (B) FISH, Dual Color Dual Fusion probe (PML-15q22 Spectrum Orange, RARA-17q21.1 Spectrum Green) showing two fusion signals (t15; 17) (q22; q21). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
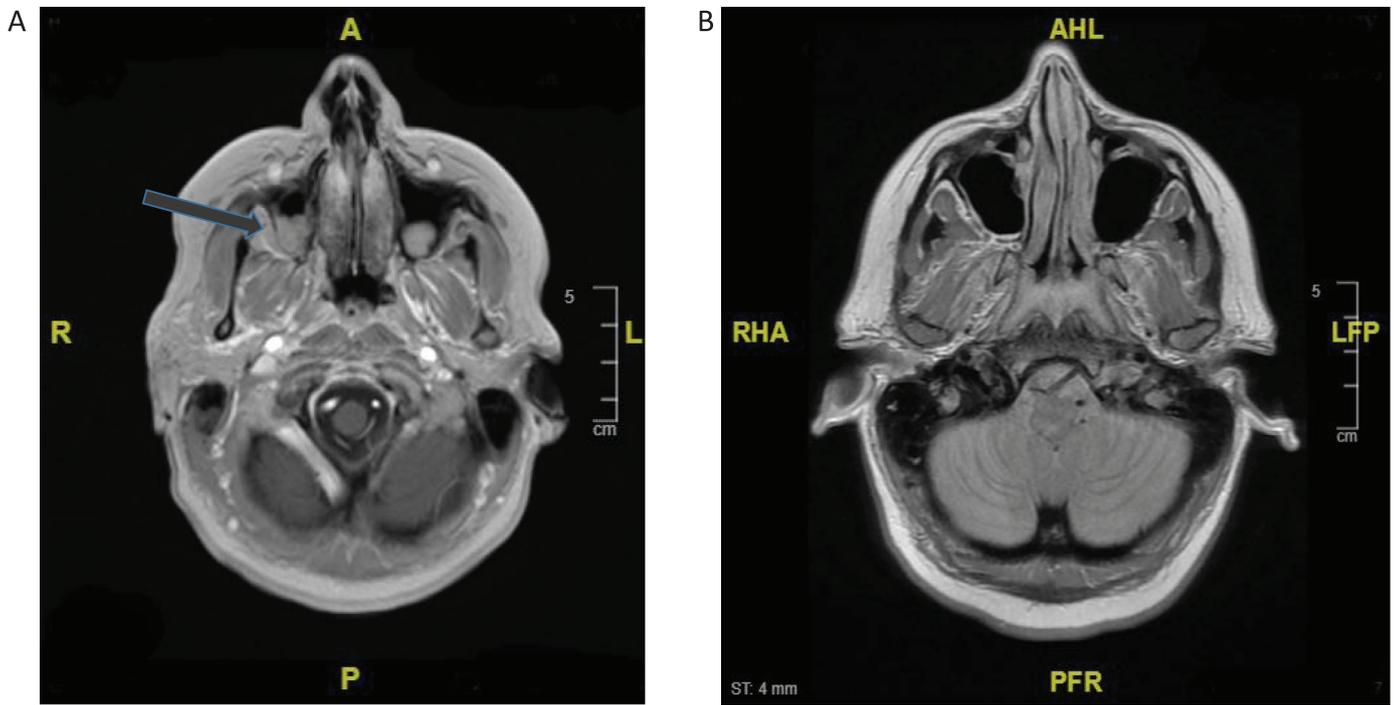
Fig. 4. Cranial MR images (A) pre-treatment MRI, infiltrative lesion involving the clivus, the right maxilla, and right mandible without evidence of intracranial bleeding. AND (B), post-treatment MRI, complete resolution of these infiltrative lesions.

distinct clinical presentations and low peripheral counts may need to be examined and risk stratified differently rather than being deemed to carry a low risk disease based on low peripheral counts.

Identification of rare presentations of APL at diagnosis, in our case, the intracranial and marrow involvement without peripheral blood involvement, is highly critical. Furthermore, the presence of packed heavily replaced marrow with APL blasts May represent additional risk.

There is lack of data on the adequacy of intracranial penetration of lower intensity therapies such as arsenic and ATRA. Such sites when involved may exempt patients from following the current risk stratification and prompt the use of more CNS directed therapy including intrathecal administration of therapeutic agents that approved for this route of administration and until CSF is adequately treated. We decided to treat our patient with chemotherapy induction using cytarabine and

A: CSF, cytology showing population of myeloid blasts
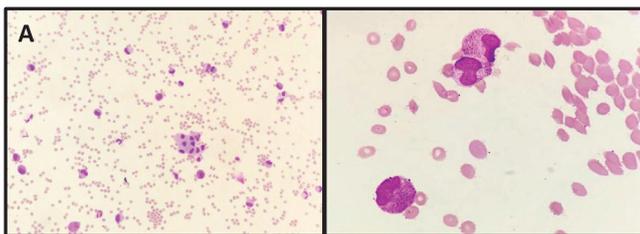
B : CSF, flow cytometry, showing a population of MPO +, CD117 dim +, CD33+, CD15-, CD64-, CD14-, CD13 dim+ population of myeloid blasts (red).
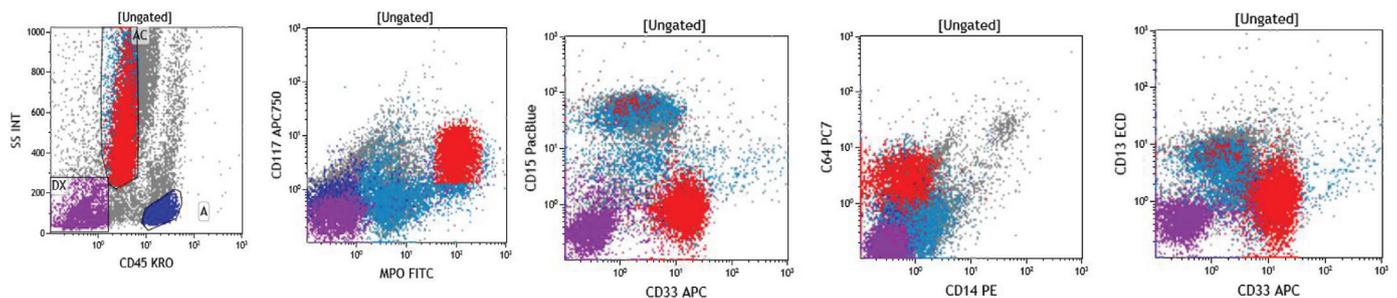
Fig. 5. (A) Cytology examination of the CSF shows the presence of malignant promyeloblasts with prominent azurophilic granules in the CSF, Thin prep, (10×); and Thin prep, (100×). (B) Flow cytometry of CS, showing a population of MPO+, CD117 dim +, CD33+, HLA-DR and TDT -, CD15-, CD64-, CD14-, CD13 dim+ population of myeloid blasts (red), Consistent with APL. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

daunorubicin (5 + 2), plus ATRA and intensive IT chemotherapy with cytarabine. We elected to further treat with arsenic and ATRA for 26 weeks and then maintain her on MTX, 6-MP and ATRA for two years [5]. Until further evidence to guide treatment of such rarer presentations, risk assessment should be at the discretion of the treating team. These additional risks may adversely and significantly affect treatment outcomes. Hence, such cases, treatment modalities and outcomes must be reported to help make supported decisions on how to treat these clinical subsets.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2019.04.007.

References

[1] D.A. Arber, A. Orazi, R. Hasserjian, J. Thiele, M.J. Borowitz, M.M. Le Beau, C.D. Bloomfield, M. Cazzola, J.W. Vardiman, The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, Blood 127 (20) (2016) 2391.

[2] J.F. Yamamoto, M.T.. Goodman, Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997-2002, Cancer Causes Control 19 (4) (2008) 379–390.

[3] G.M. Dores, S.S. Devesa, R.E. Curtis, M.S. Linet, L.M. Morton, Acute leukemia incidence and patient survival among children and adults in the United States, Blood 119 (Jan (1)) (2012) 34–43.

[4] M.A. Sanz, F. Lo Coco, G. Martín, G. Avvisati, C. Rayón, T. Barbui, J. Díaz-Mediavilla, G. Fioritoni, J.D. González, V. Liso, J. Esteve, F. Ferrara, P. Bolufer, C. Bernasconi, M. Gonzalez, F. Rodeghiero, D. Colomer, M.C. Petti, J.M. Ribera, F. Mandelli, Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups, Blood 96 (4) (2000) 1247.

[5] F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, et al., Retinoic acid and arsenic trioxide for acute promyelocytic leukemia, N Eng J Med 369 (Jul (2)) (2013) 111–121.

[6] M.A. Sanz, D. Grimwade, M.S. Tallman, B. Lowenberg, P. Fenaux, E.H. Estey, T. Naoe, E. Lengfelder, T. Büchner, H. Döhner, A.K. Burnett, F. Lo-Coco, Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet, Blood 113 (2009) 1875–1891.

[7] C. Collins, Central nervous system involvement at the time of presentation in acute promyelocytic leukemia, Pediatr. Blood Cancer 54 (2010) 603–605.

[8] M. Ji, Acute promyelocytic leukemia presenting with central nervous system involvement: a report of 2 cases, Kor. J. Lab. Med. 31 (2011) 9–12.

[9] C. Ganzel, Extramedullary disease in APL: a real phenomenon to contend with or not? Best Pract. Res. 27 (2014) 63–68.

[10] A. Furuya, Central nervous system involvement of acute promyelocytic leukemia, three case reports, Clin. Case Rep. 5 (5) (2017) 645–653.

[11] J.S. Merzaban, M.M. Burdick, S.Z. Gadhoum, Analysis of glycoprotein E-selectin ligANDs on human and mouse marrow cells enriched for hematopoietic stem/progenitor cells, Blood 118 (2011) 1774–1783.

[12] A Stucki, A.S. Rivier, M Gikic, M Monai, M Schapira, O Spertini, Endothelial cell activation by myeloblasts: molecular mechanisms of leukostasis and leukemic cell dissemination, Blood 97 (2001) 2121–2129.

[13] C Voermans, W van Heese, P. M, I de Jong, W.R Gerritsen, C.E. van der Schoot, Migratory behavior of leukemic cells from acute myeloid leukemia patients, Leukemia 16 (2002) 650–657.

[14] J.A Burger, A Spoo, A Dwenger, M Burger, D. Behringer, CXCR4 chemokine receptors (CD184) and α4β1 integrins mediate spontaneous migration of human CD34+ progenitors and acute myeloid leukaemia cells beneath marrow stromal cells (pseudoemperipolesis), Br. J. Haematol. 122 (2003) 579–589.