

Case 291

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History

A previously healthy 53 year old man presented with a three day history of a generalized petechial rash, hematuria and rectal bleeding following a flu-like illness. He had a white blood cell count of $8.85 \times 10^9/L$, hemoglobin of 12.5 g/dL and platelet count of $40,000 \times 10^9/L$ with 7% circulating blasts (Figure 1). Laboratory studies showed evidence of disseminated intravascular coagulation. A bone marrow biopsy showed 62% blasts.

Details

A Wright stained bone marrow aspirate obtained from the posterior iliac crest showed an increased number of intermediate to large sized cells with fine chromatin, irregularly shaped nuclei, moderate to abundant cytoplasm and azurophilic granules. Similar blasts were seen in the peripheral blood. (Figure 1). Auer rods were not seen.

A zinc-formalin-fixed, decalcified core biopsy, also obtained from the posterior iliac crest, showed hypercellular marrow (90%) composed mostly of large sheets of immature cells with folded nuclei and moderate to abundant cytoplasm and hypoplasia of normal hematopoietic elements (Figure 2).

Immunohistochemistry and Flow Cytometry

Cytochemistry (Figure 3): Myeloperoxidase positive, non-specific esterase (butyrate) negative

Flow cytometry (blast gate 56% of events, Figure 4): Positive: CD2(dim), CD13, CD33, CD38, CD45, CD64 (dim), CD65 and CD117. Negative: CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD14, CD16, CD19, CD20, CD22, CD34, CD56, and HLA-DR.

Cytogenetic Findings

47,XY,+8,t(15;17)(q24;q21)[20] (Figure 6)

Molecular Findings

Proximity Ligation Assay for PML-RARA fusion protein: Positive (Figure 5)

Interphase fluorescence in situ hybridization (FISH) for PML-RARA (dual fusion probes): Positive

Interesting Features/Discussion

This is a case of an acute promyelocytic leukemia (APL) with t(15;17)(q22;q12)/PML-RARA that highlights the utility of the proximity ligation assay (Olink Bioscience) in detecting the PML-RARA fusion protein. This technique combines the specificity imparted by requirement for dual antibody binding to the same molecule and the sensitivity of rolling circle amplification. It is, to our knowledge, the first application of this technology for detection of an abnormal fusion protein. This method may represent an alternative to FISH testing that can be performed in a routine immunohistochemistry laboratory, providing same-day results using bright-field microscopy.

The patient was treated immediately on admission with vitamin K and transfusion of platelets, fresh frozen plasma and cryoprecipitate. Upon diagnosis of acute promyelocytic leukemia, therapy with tretinoin was initiated. Within the next day, he became increasingly short of breath with low oxygen saturation. He developed an altered mental

status and left hemiplegia. Brain CT revealed intraparenchymal hemorrhage involving the right frontal and parietal lobes and extending into the ventricles. A chest radiograph revealed bilateral, multifocal opacities. Systemic corticosteroids were started in consideration of so-called differentiation syndrome. The patient's clinical condition rapidly deteriorated. Brain death was declared, and he expired shortly after being removed from the ventilator.

Proposed Diagnosis

Acute promyelocytic leukemia with t(15;17)(q22;q12)/PML-RARA.

Consensus Diagnosis

Acute promyelocytic leukemia with t(15;17)(q22;q12)/PML-RARA