Myeloperoxidase Deficient Acute Promyelocytic Leukemia: Report of Two Cases

Pulkit Rastogi¹ · Saniya Sharma¹ · Sreejesh Sreedharanunni¹ · Prashant Sharma¹ ·
Man Updesh Singh Sachdeva¹ · Richa Jain² · Shano Naseem¹ · Amit Trehan² ·
Neelam Varma¹

Received: 30 March 2017 / Accepted: 27 June 2017 / Published online: 4 July 2017
© Indian Society of Haematology & Transfusion Medicine 2017

Acute promyelocytic leukemia (APL) is characterized by the presence of ‘abnormal promyelocytes’ which show variable morphology but a characteristic strong myeloperoxidase (MPO) positivity on cytochemistry and immunohistochemistry (IHC). The characteristic morphology and cytochemistry is often considered as a strong evidence to make a morphological diagnosis of APL and often enough to prompt a haematologist to start all-trans-retinoic acid (ATRA), before a confirmatory molecular diagnosis

arrives. We herein describe two cases of classical APL having an absent/reduced MPO activity.

Case 1 A 6-year-old male child presents with history of ecchymosis and pallor. His complete blood count revealed pancytopenia (hemoglobin—82 gm/L, leukocyte count— $4.1 \times 10^9/L$ and platelet count— $19 \times 10^9/L$). There were 40% abnormal promyelocytes in peripheral blood and 79% in bone marrow with occasional faggot cells. The findings were highly suspicious of APL, but the promyelocytes were negative for MPO on cytochemistry, IHC and flow-cytometry (Fig. 1). However, reverse transcriptase-polymerase chain reaction (RT-PCR) demonstrated the presence of bcr1 isoform of *PML-RARA* fusion transcript confirming the diagnosis of APL.

Case 2 A 10-year-old male child presented with fever, pallor, gum hypertrophy and hepatosplenomegaly. Hemogram revealed leucocytosis and bicytopenia (Hb—111 gm/L leukocyte count— $73.9 \times 10^9/L$, platelet count— $43 \times 10^9/L$). There were 95% abnormal promyelocytes in peripheral blood and 94% in bone marrow. The morphology was suspicious of APL, but MPO cytochemical stain was only weakly positive in approximately 20% of promyelocytes despite repeated attempts; and after excluding technical issues. Flowcytometric findings were not classical of APL (Fig. 2). A morphological diagnosis of APL could not be offered. However, RT-PCR for *PML-RARA* fusion transcript showed positivity for bcr3 isoform.

A morphological diagnosis of APL can be challenging in cases with variant morphology. However, a strong MPO cytochemical reaction is often the clue to its diagnosis even such cases. MPO negativity often leads to an alternate diagnosis like monocytic leukemias. However, one of the pitfalls of relying on this simple cytochemical stain/IHC is

✉ Sreejesh Sreedharanunni
sreejesh.s@pgimer.edu.in

Pulkit Rastogi
drpulkitrastogi@gmail.com

Saniya Sharma
drsaniya.sharma@gmail.com

Prashant Sharma
prashant.sh@gmail.com

Man Updesh Singh Sachdeva
drmanupdeshpgi@yahoo.co.in

Richa Jain
docrichajain@yahoo.com

Shano Naseem
shanonaseem@yahoo.co.in

Amit Trehan
amita9111@gmail.com

Neelam Varma
varmaneelam@yahoo.com

¹ Department of Hematology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

² Department of Pediatric Hematology/Oncology Unit, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Fig. 1 Case 1: **a** Abnormal promyelocytes showing multiple Auer rods (MGG stain, $\times 1000$); **b** Myeloperoxidase cytochemical stain showing negativity in abnormal promyelocytes. A neutrophil with positive reaction can be seen. Inset shows MPO negative Auer rods as negative linear shadows (haematoxylin counterstain, $\times 1000$); **c** MPO immunostain on trephine biopsy depicting absence of staining in

majority of the cells (hematoxylin counterstain, $\times 1000$). **d–i** Flow cytometry showing classical immunophenotype suggestive of APL ($CD34^{Neg}$, $HLA-DR^{Neg}$, $CD13^{Heterogeneous\ pos}$, $CD33^{Bright\ pos}$) but with lack of high side scatter and negativity for MPO. The cells were negative for CD15 (not shown) and CD56 (Inset shows findings from the cells stained only for CD45)

an inherent MPO deficiency seen very rarely in the population. This together with atypical flow cytometric findings can lead to a wrong diagnosis.

Cui et al. [1] have described two cases of adult APL (both microgranular variant) with absent or reduced MPO activity. A third case was described by Heiblig et al. [2] where an extensive molecular analysis revealed germline heterozygous *MPO* gene mutation. Uniparental disomy of 17q chromosome, where the *MPO* gene is located, has

resulted in a homozygous MPO deficiency. MPO enzyme deficiency is a rare autosomal recessive condition resulting from missense mutations and predisposes individuals to candida infections [3–5]. The absent/reduced MPO activity in our cases may be due to the same mechanism or due to some other unknown mechanisms.

The cases are being reported due to the extreme rarity of MPO negative APLs. The cases reinforce the dictum that morphological evaluation continues to be important; and

Fig. 2 Case 2: **a** Abnormal promyelocytes showing cleaved nucleus and granulated cytoplasm. Auer rods were not seen (MGG stain, $\times 1000$); **b** Myeloperoxidase stain showing weak positivity (haematoxylin counterstain, $\times 1000$); **c** Trephine biopsy showing sheets of immature myeloid cells. **d–i** Flow cytometry showing absence of high

side scatter, autofluorescence, $CD34^{Pos}$, $HLA-DR^{Pos}$, $CD13^{Pos}$, $CD33^{Pos}$, $CD117^{Pos}$, $CD56^{neg}$ and MPO^{Neg} immunophenotype. The cells were also positive for CD9—not shown (*Inset* shows findings from the cells stained only for CD45)

PML-RARA or its equivalent should be tested in all patients even with the slightest morphological suspicion.

Compliance with Ethical Standards

Conflict of interest All authors declare that they do not have any conflict of interest.

Ethical Statement This article does not contain any studies with human participants or animals performed by any of the authors. The article does not include any identifying information of any individual.

References

1. Cui W, Qing S, Xu Y et al (2002) Negative stain for myeloid peroxidase and Sudan black B in acute promyelocytic leukemia

(APL) cells: report of two patients with APL variant. *Haematologica* 87:ECR16

2. Heiblig M, Paubelle E, Plesa A et al (2017) Comprehensive analysis of a myeloperoxidase negative acute promyelocytic leukaemia. *Blood* 129:128–131
3. Marchetti C, Patriarca P, Solero GP, Baralle FE, Romano M (2004) Genetic characterization of myeloperoxidase deficiency in Italy. *Hum Mutat* 23:496–505
4. Borregaard N, Boxer LA (2016) Disorders of neutrophil function. In: Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT (eds) *Williams hematology*, 9e. McGraw-Hill, New York
5. Hansson M, Olsson I, Nauseef WM (2006) Biosynthesis, processing, and sorting of human myeloperoxidase. *Arch Biochem Biophys* 445:214–224