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CASE REPORT PEER REVIEWED | OPEN ACCESS

Multiple genetic mutation and aberrant loss of CD16 in a patient with neutropenia

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ABSTRACT

We report a case of a patient with neutropenia and loss of CD16 in mature neutrophils as well as its novel correlation with persistent SH2B3 mutation with high variant allele fraction.

Keywords: CD16, Flow cytometry, Next generation sequencing, SH2B3

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INTRODUCTION

Flow cytometric studies performed on the peripheral blood are a widely available assay that can detect clonal lymphoid populations as well as blast population. Next generation sequencing (NGS) is a DNA-based technology and is resource-intensive but can detect genetic abnormalities. We report a case of a patient with neutropenia, initial discovery of flow cytometric finding (loss of CD16 on the neutrophils) which then prompted further evaluation of NGS revealing SH2B3. CD16 is normally expressed by mature neutrophils, which may act as an adhesion structure to bind immune complexes. Loss of expression of CD16 by mature neutrophils is abnormal and is previously associated with genetic deficiency, paroxysmal nocturnal hemoglobinuria as well as sepsis [1, 2]. Mutations of high allelic burden may be associated with myeloid neoplasms. This relationship between the loss of CD16 and SH2B3 is novel and is detailed in this report.

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CASE REPORT

The patient is a 47-year-old woman status post bilateral mastectomy following breast cancer. She was diagnosed three years ago and refused chemotherapy but received tamoxifen and radiotherapy. Complete blood count analysis revealed decreased white blood cell count (3300/uL) with absolute neutrophil counts of 1600/uL. Polychromatic flow cytometric analysis demonstrates aberrant loss of CD16

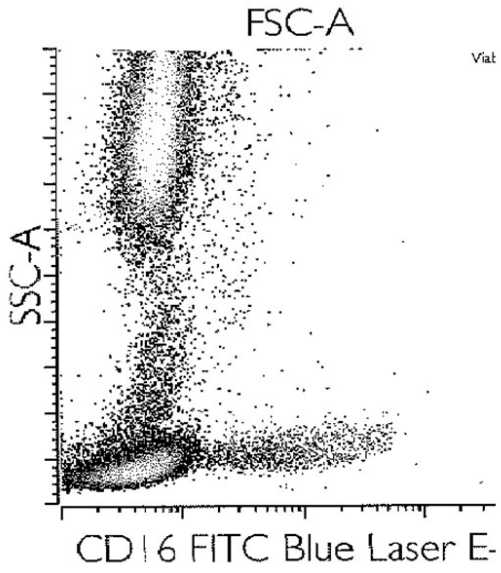

Figure 1: Histogram displaying loss of peripheral blood CD16 within the granulocytes with high side scatter. CD16 is noted within the NK cells with low side scatter.

within mature neutrophils (Figure 1). Next generation sequencing (NGS) revealed persistent SH2B3 with high variant allele burden. Bone marrow studies reveal no increased blasts or morphologic dysplastic changes.

DISCUSSION

The normal neutrophils display specific antigen expression patterns that are characteristically observed in healthy individual; abnormal cell populations can reveal distinct gain or loss of antigens [3]. CD16 is normally expressed by mature neutrophils and is a low affinity Fc gamma receptor III. On the neutrophils, CD16 may act as an adhesion structure to bind immune complexes for activation but not enable antibody dependent cell-mediated cytotoxicity that is seen in NK cells [3–5]. Loss of CD16 is a neutrophil abnormality and has been reported in association with genetic deficiency of CD16 [6], in association with paroxysmal nocturnal hemoglobinuria and in acquired immune deficiency syndrome [1] as well as sepsis [2].

In recent years, NGS studies have been helpful in characterizing myeloid disorders such as myelodysplasia, acute myeloid leukemia as well as potential risk factor for cardiovascular disease. Next generation sequencing performed on this patient demonstrated multiple high frequency mutations including, SH2B3, (VAF) of 24.2% in the peripheral blood and 18.6% in the marrow.

SH2B3 encodes a membrane associated adaptor protein that negatively regulates signal transduction initiated by growth factor and cytokine receptor kinases [7].

Clonal hematopoiesis of indeterminate potential (CHIP) is associated with increased risk of cardiovascular disease and minimal risk of progression to myeloid or lymphoid neoplasm. The variant allele fraction (VAF) is typically below 10% in CHIP. The VAF found in this patient is too high to attribute it to CHIP. Interestingly, chemotherapy may increase the risk of developing therapy-related myeloid neoplasm in presence of CHIP. However, this patient never received chemotherapy. Recently, idiopathic cytopenia of undetermined significance (ICUS) has been proposed to describe unexplained cytopenia that does not satisfy the diagnosis of myelodysplasia [8, 9]. Furthermore, clonal cytopenia of undetermined significance (CCUS) has been proposed to classify patients with ICUS as well as one or more mutations. The findings of in this patient best fit the description for ICUS and/or CCUS.

CONCLUSION

The combined constellation of findings (neutropenia, loss of CD16 in neutrophils, and persistent SH2B3 mutation with modest variant allele burden) in the currently described case is a novel contribution to the literature. In particular, flow cytometrically detectable loss of CD16 on neutrophils is uncommon but may serve as indicator for further genetic testing.

REFERENCES

1. Boros P, Gardos E, Bekesi GJ, Unkeless JC. Change in expression of Fc gamma RIII (CD16) on neutrophils from human immunodeficiency virus-infected individuals. Clin Immunol Immunopathol 1990;54(2):281–9.
2. Wagner C, Deppisch R, Denefleh B, Hug F, Andrassy K, Hänsch GM. Expression patterns of the lipopolysaccharide receptor CD14, and the FCgamma receptors CD16 and CD64 on polymorphonuclear neutrophils: Data from patients with severe bacterial infections and lipopolysaccharide-exposed cells. Shock 2003;19(1):5–12.
3. Wang L, Wells DA, Deeg HJ, Loken MR. Flow cytometric detection of nonneoplastic antigenic polymorphisms of donor origin after allogeneic marrow transplant: A report of two cases. Am J Clin Pathol 2004;122(1):135–40.
4. Lanier LL, Ruitenberg JJ, Phillips JH. Functional and biochemical analysis of CD16 antigen on natural killer cells and granulocytes. J Immunol 1988;141(10):3478–85.
5. Graziano RF, Fanger MW. Fc gamma RI and Fc gamma RII on monocytes and granulocytes are cytotoxic trigger molecules for tumor cells. J Immunol 1987;139(10):3536–41.
6. Wagner C, Hänsch GM. Genetic deficiency of CD16, the low-affinity receptor for immunoglobulin G, has no impact on the functional capacity of polymorphonuclear neutrophils. Eur J Clin Invest 2004;34(2):149–55.
7. Maslah N, Cassinat B, Verger E, Kiladjian JJ, Velazquez L. The role of LNK/SH2B3 genetic alterations in myeloproliferative neoplasms and other hematological disorders. Leukemia 2017;31(8):1661–70.
8. Gillis NK, Ball M, Zhang Q, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: A proof-of-concept, case-control study. Lancet Oncol 2017;18(1):112–21.
9. Valent P, Orazi A, Steensma DP, et al. Proposed minimal diagnostic criteria for myelodysplastic syndromes (MDS) and potential pre-MDS conditions. Oncotarget 2017;8(43):73483–500.

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Author Contributions

Safina Hafeez – Design of the work, Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Peter UF Shen – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Drafting

the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
The corresponding author is the guarantor of submission.

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.