Case Report

Pseudo-Pelger-Huët Anomaly in Association with Tacrolimus and Mycophenolate Mofetil in a Kidney Transplant Patient

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Abstract

Background: Pelger-Huët anomaly is a congenital or acquired anomaly characterized by neutrophil nuclear hyposegmentation and excessively condensed chromatin.

Case: We reported a case of 61-year-old women who developed acquired Pelger-Huët anomaly following kidney transplantation while on immunosuppressive medications tacrolimus and mycophenolate mofetil. The neutrophils resumed their normal segmentation after medication dose reduction.

Conclusion: These medications have been associated with this abnormality previously. In our case, the Pelger-Huët anomaly may be the result of the combination of these two drugs or tacrolimus alone.

Keywords: Pelger-Huët anomaly, Tacrolimus, Mycophenolate Mofetil

Introduction

Pelger-Huët anomaly (PHA) was firstly described in 1928 by Dr. Kraj Pelger [1], and it was further recognized as a benign autosomal dominant trait in 1931 by Dr. G.J. Huët [2]. The hereditary anomaly is characterized by excessive condensed chromatin and hyposegmentation of granulocyte nucleus. The nuclear shape can be round, oval unilobed in homozygotes and coffee bean-shaped or symmetrically bi-lobed in heterozygous state [3,4]. The granulocytes with Pelger-Huët anomaly have a normal life span and their function appears to be normal. Pseudo Pelger-Huët anomaly (PPHA) is an acquired neutrophilic anomaly which can be induced by many medications as well as myeloid neoplasms, such as acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms. It has also been associated with Addison disease, Rheumatoid arthritis, parvovirus, and mycoplasma [5-8]. Certain drugs like tacrolimus, Mycophenolate Mofetil (MMF), ganciclovir, co-trimoxazole, itraconazole fludarabine, rituximab, citalopram, lorazepam, nomifensine, ibuprofen, sulfonamide, D-penicillamine, colony stimulating factor, and interleukin-5 have been reported to be associated with inducement of PPHA [5]. PPHA induced by medications usually shows more homogeneous unilobed nuclei than those of PHA, and this neutrophilic abnormality is reversible following dose reduction and medication discontinuation [6-8].

The underlying mechanism of PPHA still remain unclear. Some hypotheses concluded that PPHA was associated with a genetic defect in the lamina B receptor on chromosome 1q41-q43 [9], increased incidence of 17p deletions [9], or maybe a manifestation of apoptosis [9,10]. However, the mechanism of PPHA caused by
immunosuppressive agents seems to be associated with inhibition of guanosine nucleoside synthesis [11] and a direct toxicity by alteration of metabolism of cytochrome P450 [12,13]. In this report, we described a case of PPHA in a kidney transplant recipient in whom the acquired Pelger-Huët anomaly was associated with the combination of the immunosuppressive drugs tacrolimus and MMF or tacrolimus alone.

Case Report

A 61-year-old woman with history of chronic pancreatitis, Type II diabetes mellitus, hypertension, fatty liver, and mitral valve prolapse, who was 4-months post kidney transplant, presented with mild chronic anemia and moderate to marked neutropenia. The patient was on multiple medications, including tacrolimus and MMF following kidney transplant. She was referred to the hematology clinic for follow-up given the cytopenias. At the time of pathologic evaluation, the patient was receiving tacrolimus 3 mg twice a day, as well as MMF 500 mg twice a day. Her blood smear was referred for pathologist review because of the presence of dysplastic neutrophils. Automated blood cell count included white blood cell count (WBC) 0.8 × 10^9/L, red blood cell count (RBC) 3.94 × 10^12/L, Hemoglobin (Hgb) 11.6 g/dL, Haematocrit (Hct) 36.3%, mean corpuscular volume(MCV) 92.2 fl, Mean Corpuscular Hemoglobin (MCH) 29.4 pg, Mean Corpuscular Hemoglobin Concentration (MCHC) 31.9 g/dL, Red Blood Cell Distribution Width (RDW) 13.5%, platelet 102 × 10^3/uL, and Mean Platelet Volume (MPV) 10.2 fl. Manual white blood cell differential included 67% neutrophils, 25% lymphocytes, 7% monocytes, and 1% reactive lymphocyte.

Review of the blood smear revealed slight anisopoikilocytosis of red blood cells with some ovalocytes and a few teardrop cells. It also revealed a significant absolute neutropenia with neutrophils having appropriate granulation, but atypical, coarse, waxy chromatid and atypical nuclear shape including round, oval, coffee-bean, and bi-lobed. The majority of neutrophils demonstrated this Pelger-Huët anomaly (Figure 1).

Many neutrophils resumed their normal segmentation with a left shift one week later (Figure 2). Automated blood cell count included WBC 2.7 × 10^9/L, RBC 4.03 × 10^12/L, Hgb 12.2 g/dL, Hct 37.2%, MCV 92.2 fl, MCH 30.2 pg, MCHC 32.8 g/dL, RDW 14.0%, platelet 88 × 10^3/uL, and MPV 11.2 fl. Manual white blood cell differential included
43% segmented neutrophils, 18% band neutrophils, 7% metamyelocytes, 4% myelocytes, 14% lymphocytes, 11% monocytes, and 2% reactive lymphocytes. Red blood cell morphology showed slight poikilocytosis with few ovalocytes and tear drop cells. Pelger-Huët changes persisted for six weeks while the patient received 7 mg of tacrolimus and 750 mg of MMF twice a day. Tacrolimus and MMF doses were gradually decreased over time. MMF was discontinued for three days due to neutropenia. Tacrolimus blood level has been monitored for twenty-six weeks since three days after transplantation (Figure 3). Follow-up complete blood count with differential was completely normal after two months.

Figure 2: Many of the neutrophils in the kidney transplant recipient resumed their normal segmentation after dose reduction of tacrolimus and MMF.

Figure 3: Tacrolimus blood level monitoring since transplantation. PPHA was observed between twelve weeks and eighteen weeks after transplantation in this patient.
Conclusion

In the present case, PPHA was associated with either the combination of the two immunosuppressive agents or tacrolimus alone. This assumption was supported by the facts that the initial dysplasia occurred 3 months after transplantation and resolved with decreasing medication dosage. The dosage of tacrolimus was decreased from 7 mg to 2-4 mg twice a day, and MMF was reduced from 750 mg to 250 mg twice a day and discontinued for three days due to neutropenia. Therefore, the appearance of PPHA seems to correlate with introduction of tacrolimus and MMF, and subsequent normalization of neutrophilic nuclear segmentation could be due to their dose reduction and discontinuation. However, spontaneous improvement of hematologic abnormalities cannot be completely excluded, but this is not favoured given significant correlation with medication timeline and dose adjustment as well as previous associations between immunosuppressive medications and PPHA noted in the literature. Further tests were needed to confirm the association between the PPHA and immunosuppressant medications.

The presence of PPHA is currently considered to be the one of the more specific morphologic findings for the diagnosis of myelodysplastic syndrome, with micromegakaryocytes being more specific. However, some patients receiving immunosuppressive drugs, or other medications, may present with this PPHA appearance. Laboratory professionals and clinicians should be aware of this possible abnormality in circulating-neutrophils and avoid diagnostic confusion, especially for those patients receiving graft transplantation and immunosuppressive therapy. To differentiate between hereditary and acquired PHA, review of clinical findings is essentially (i.e. time of onset compared with medication history). To differentiate PPHA due to medications versus myelodysplastic syndrome, morphologic review of cytoplasmic granularity is suggested as medication induced PPHA will usually maintain normal cytoplasmic granulation. In patients with suspected medication induced PPHA, clinical follow-up with peripheral blood smears would be appropriate. In conclusion, it is necessary to recognize the potential benign nature of PPHA to avoid unnecessary diagnostic intervention and medical treatment.

References


