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Case Report

A case of severe bone-marrow suppression due to azathioprine in a patient of kidney transplant

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ABSTRACT

Azathioprine is one of the members of the standard triple therapy of immunosuppressive agents used in patients of renal transplant. Azathioprine is being used successfully in majority of patients with renal graft. But one of the dreaded complications caused by it is severe bone-marrow suppression. Here I am reporting a case of severe, life- threatening bone-marrow suppression in a 30 years old male patient of renal transplant. The case is very important and attention is needed to be given by health care professionals and by clinicians. The patient underwent renal transplant surgery in Indraprastha Apollo hospital, New Delhi. The patient was on immunosuppressive agents: prednisolone, cyclosporine and mycophenolate mofetil. After 10 months of renal transplant surgery, the patient was switched over azathioprine due to complains of GI upset probably due to mycophenolate mofetil. In initial 2 months there was moderate bone-marrow suppression, but afterwards there was severe bone-marrow suppression. Lastly TLC reached 300 /mm^3 and Hb was 3.8 g/dL and that was life-threatening condition. The patient was managed in ICU with inj. Grafeel under strict hygienic conditions. The patient was recovered successfully with the help of necessary conservative managements during admission. In my case, causality of azathioprine was "definite/ certain" as per Naranjo scale. Seriousness of the reaction was "life- threatening".

Keywords: Azathioprine, Bone-marrow suppression, Renal transplant

INTRODUCTION

Azathioprine is one of the major immunosuppressive agents used to prevent rejection following renal transplantation. Other immunosuppressive agents used are mycophenolate mofetil, cyclosporine and prednisolone. One of the most important and feared side- effects of azathioprine is bone-marrow suppression, reported in 14-35% of patients.[1] This usually recovers following withdrawal of the drug or reduction in dose. Leucopenia is the commonest manifestation and is reported among 96% those developing myelosuppression. Anaemia in 60% and thrombocytopenia in 30% of these cases.[2]

Usually the bone-marrow suppression is mild and recovers following withdrawal of the drug or reduction in dose of the drug. But some-times in few patients, azathioprine causes severe life- threatening bone-marrow suppression leading to hospitalisation. Infections remain the major risk during the phase of leucopenia. Presence of pancytopenia, graft dysfunction, severe leucopenia (<2000 /mm^3), fever, and sepsis prognosticate a dismal outcome.[3]

Here we are showing a pattern of development of severe bone-marrow suppression due to azathioprine in a patient having renal graft along with its causality assessment.

CASE REPORT

A 30 years old male patient underwent renal transplant surgery in march, 2019 in Indraprastha Apollo hospital, New Delhi. He was on immunosuppressive agents-

prednisolone, cyclosporine and mycophenolate mofetil in usual adult doses. Due to complaints of GI upset and loss of appetite, he reported to his nephrologist on 24/12/2019. His nephrologist started tablet Azathioprine, 50 mg, OD in place of mycophenolate mofetil. Haemoglobin, total RBC, TLC and total platelet count gradually decreased after starting azathioprine.

The baseline blood parameters as on 24/12/2019 were: Hb: 12.30 g/dL, TLC: $8.10\times10^3/mm^3$, total RBC count: 3.95 mill/mm^3, total platelet count: $196.0\times10^3/mm^3$

RESULTS

After 24/12/2019, the patient was on tablet Azathioprine, 50 mg, OD. As the patient was on regular follow up, CBC and renal function test were done on 19/01/2020. On 19/01/2020, the blood parameters were as follows: Hb: 9.30 g/dL, TLC: 5.20×10^3/ mm^3, platelet count: $273.0\times10^3/mm^3$, RBC count:3.12 mill/mm^3

The above data shows decreased Hb, RBC count and TLC. At that time, it was not confirmed that the culprit was azathioprine. The nephrologist continued azathioprine and in February 2020 there was severe bone-marrow suppression. The blood parameters changed as given in Table 1.

Table 1: Variation in CBC after starting Azathioprine.

Date	Hb (g/dL)	RBC count	TLC	Platelet count
24/12/2019	12.30	3.95	8.10	196
19/01/2020	9.30	3.12	5.20	273
10/02/2020	8.80	2.87	5.70	271
24/02/2020	7.50	2.40	1.50	210
27/02/2020	6.30	1.98	1.19	160
28/02/2020	5.60	1.76	1.00	137
29/02/2020	3.80	1.02	0.30	95

Units of RBC count=mill/mm^3, TLC=$\times10^3/mm^3$, platelet count=$\times10^3/mm^3$.

As viral infection of the renal graft and bone-marrow could also lead to bone-marrow suppression, cytomegalovirus and Epstein- barr virus PCR test were also done. But result of both of them were negative.

The nephrologist stopped the azathioprine on 25/ 02/2020 and gave inj. Grafeel, 300 mcg, S/C, stat. He advised to continue same dose of inj. grafeel for next 4 days and told to do daily evaluation of CBC.

The Hb, RBC count, TLC and platelet count continued to decrease and the patient was admitted in emergency department of Indraprastha Apollo hospital, New Delhi on 29/02/2020. The patient was kept under extreme hygienic conditions and vitals were monitored. Inj. Grafeel was continued. In the hospital CBC report was: Hb: 3.8 g/dL, TLC:$300/mm^3$, RBC count: 1.02 mill/ mm^3, total platelet count:$95\times10^3/mm^3$.

The inj. Grafeel was continued and 3 units of whole blood transfusion was done after blood grouping and cross-matching. The sensorium of the patient was also started deteriorating like loss of recent memory and it continued for 2 days. TLC was $300/mm^3$, total platelet count was $95\times10^3/mm^3$ and Hb was between 4.0-4.5 g /dL for 2 days in spite of 3 units of blood transfusion. But in next day the sensorium was slightly improved with TLC=$400/mm^3$. The TLC again improved to $600/mm^3$ next day followed by $1000/mm^3$ on subsequent next day.

After that, 3 units of platelet transfusion was also done on next 3 consecutive days as total platelet count was $15\times10^3/mm^3$ in spite of 3 units of whole blood transfusion during the hospital admission. The peak suppression in total platelet count was after the peak suppression of RBC and TLC count. The platelet counts also showed improvement in sequence: 15×10^3, 21×10^3, 29×10^3 and $35\times10^3/mm^3$ on subsequent days after platelet transfusion.

The patient was discharged on 09/03/2020 when appropriate blood parameters were obtained- Hb:7.4 g/dL, TLC: $3,000/mm^3$, RBC count: 2.43 mill/mm^3, total platelet count: $41\times10^3/mm^3$

In my case, causality of azathioprine was “definite/ certain” as per Naranjo scale. Seriousness of the reaction was “life- threatening”.

DISCUSSION

Azathioprine is a nitroimidazole derivative of 6-mercaptopurine. The drug inhibits both DNA and RNA synthesis and recent studies indicate that the immunosuppressive action of the drug results predominantly from a block in the production of interleukin-2.[4] Bone-marrow suppression due to this drug is reported in 14-35% patients.[5] A recent study from India reported bone-marrow suppression in 14.3% of their patients.[2] Three phases of azathioprine induced bone-marrow suppression have been described: stage of megaloblastic erythropoiesis, stage of defective granulopoiesis, and stage of toxic panmyelopathy.[6] Pollock observed that all his patients who developed myelo-suppression did so in the first 8 weeks of azathioprine exposure with a mean period of 3.6 weeks.[7] However, a report from India observed immune-suppression after an average exposure of 16.3 months.[2] Most western research workers found recovery within 2 weeks of stoppage of the drug while an Indian study found bone-marrow recovery in a mean of 2.6 months.[2] In my case myelosuppression started in first 4 weeks of azathioprine exposure and it recovered within 2 weeks after stoppage of azathioprine under support of inj Grafeel. The bone-marrow suppression was severe and life-threatening. The patient was kept in ICU for 10 days and was discharged successfully.

CONCLUSION

As azathioprine is safe in normal recommended doses, but proper monitoring of CBC is necessary to avoid the bone-marrow suppression, which may be lethal enough to cause death. Severe leucopenia (<2000/mm^3) is the most dreaded complication leading to sepsis. Grafeel 300 mcg injection, a human granulocyte colony-stimulating factor (G-CSF) is used to treat myelosuppression and prevents sepsis. In case of severe sepsis, hospital admission is must. In ICU, daily monitoring of vitals and CBC are done and blood transfusion is also done when required.

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