International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor (2018): 7.426

Azathioprine Induced Septicemia and Pancytopenia

Ameez S Khan[1], Vidya V Nair[2], Dr. Ganesan M.[3]

[1, 2]Department of Pharmacy Practice, Al Shifa College of Pharmacy, Poonthavanam.679325, Perinthalmanna, Kerala, India

[3]Consultant Nephrologist, KIMS AL Shifa Pvt Ltd Hospital, Perinthalmanna, Malappuram.679322, India

1. Background

Azathioprine, a prodrug of 6 mercaptopurine, is an immunosuppressant that can be used as adjunctive therapy with other immunosupressants to prevent graft rejection and also to treat various autoimmune diseases. Azathioprine is a widely used immunosupressant introduced into clinical practice in 1960s for kidney transplant recipients. Major side effects of azathioprine include hepatotoxicity, hematological toxicities, myalgia and increased susceptibility to infection. Myelosupression is known to occur with it, but severe pancytopenia and sepsis are uncommon. The genetic polymorphism of enzyme Thiopurine S Methyltransferase (TPMT) can lead to this excessive drug toxicity[1].

2. Case Report

A 44 year old male patient with long standing CKD, who underwent kidney transplant 10 years ago, he has been on regular outpatient follow up until a year ago and lost follow up for past 1 year. His last serum creatinine was around 3 mg/dl a year before. Thereafter, he was following up elsewhere and was taking Tab. AZORAN (Azathioprine) 50 mg BD and Tab. WYSOLONE (Prednisolone) 20 mg OD. Apparently a month ago, he developed intermittent high grade fever, easy fatigability, decreased urine output. He was found to have azotemia, uremic symptoms, anemia, volume overload, lethargic dyspnoeic class 4 and a positive blood culture and sensitivity report with presence of Burkholderia cepacia (fig: 1). He had functioning left raduicocephalic AV fistula and canulated for Haemodialysis. He was given with minimal immunosuppressive therapy and he has received Meropenem 500 mg IV BD for 1 week and Vancomycin 1gm iv after each haemodialysis to treat sepsis.

Fever settled with meropenem, but after 1 week, fever reappeared and patient admitted with anemia, edema bilateral pleural effusion in right, ascites echymoses and euhydrated. Complete blood counts shown to be markedly reducing. (fig :2)Tab AZORAN has been stopped and antibiotics continued for sepsis, fever subsided using Tab. DOLO (Paracetamol) 650 mg. He received 3 units of packed red cell transfusion and Tab PANGRAF (Filgrastim) 1 ampule OD till blood counts were on normal limit. On discharge the total blood counts are found to be improving and patient became stable and oriented. On next follow up, complete blood counts were in normal range.

Blood Culture and Sensitivity	
Nature of specimen :	Blood
Organism isolated:	**Burkholderia cepacia**
Sensitive antibiotics	
Meropenem	MIC = 1
Ticarcillin+Clavulanic acid	MIC =16
Ceftazidime	MIC =4
Levoflox	MIC =2
Minocycline	MIC =2
Trimethoprim+Sulphamethoxazole	MIC <=20

Figure 1: Laboratory Findings during Hospital Stay

Test	Day 1	Day 2	Day 3
Haemoglobin	8g/dl	10.3g/dl	10.3g/dl
Total WBC	1.30X1000c/cu	6.00x1000c/cu	11.40X1000c/cu
RBC	3.05 million c/cu	3.54 million c/cu	3.6 million c/cu
PCV	23.2%	27.1%	30.5%
Polymorph	78%	80%	81%
Lymphocyte	13%	13%	15%
Platelet count	18x1000 c/cu	16.1000 c/cu	21x1000 c/cu
PDW	19.2%	17.6%	18.4%
PCT	0.01%	0.01%	0.02%

Figure 2

3. Discussion

The metabolism of azathioprine is now better understood. *In vivo*, it is converted, non-enzymatically, to 6-mercaptopurine. Further metabolism of this drug involves various enzymes like, hypoxanthine guanine phosphoribosyl transferase (HGPRT), thiopurine methyltransferase (TPMT), and xanthine oxidase (XO). HGPRT is responsible for its bio-activation and converts it to 6-thioinosine 5-monophosphate which is further metabolized to 6-thioguinine nucleotides (6-TGNs). 6-GTNs get incorporated into DNA and RNA and are possibly, responsible for cytotoxic effect. Another mechanism suggested involve 6-GTNs binding to GTPase Rac 1 leading to activation of mitochondrial pathway of apoptosis in CD3 and CD28 co-stimulated T-cells. [2] Both XO and TPMT are catabolic enzymes involved in clearance of thiopurines. Xanthine oxidase is inhibited by allopurinol and concurrent administration of both allopurinol and azathioprine can lead to enhanced azathioprine toxicity. TPMT-dependent catabolism is critical, as low TPMT activity may lead to enhanced cytotoxicity. TPMT is governed by a genetic polymorphism and is responsible for the differential susceptibility to myelosupression.

The patient in this case report experienced severe complications. AZA has been used in allograft patients, often along with steroids, as in our case. Reports on adverse events of AZA in patients with organ transplantation are

few; on the other hand, there are many reports on myelosuppression after AZA in patients with other autoimmune diseases, such as inflammatory bowel disease and systemic lupus erythematosus (SLE) (4); Gizbert et al. reported that six out of 73 SLE patients receiving AZA developed leukopenia and required a dose reduction or discontinuation of the medication. Three of these patients had reversible pancytopenia, and two tolerated the reduced AZA dose. In patients with inflammatory bowel disease, pancytopenia was reported in 0.4-2% of the cases treated with AZA (5). In our case, myelosuppression was detected 1 year after introduction of AZA. Similarly, myelosuppression has been reported to occur within 8 to 70 days after AZA is administered.

4. Conclusion

This patient represents a probable case of azathioprine-induced severe pancytopenia and sepsis with a Naranjo probability score of 8. Clinical vigilance and close laboratory follow up are needed to avoid the possibility of sepsis and pancytopenia in long term prescribing of azathioprine for immunosupression.

References

[1] Patel AA, Swerlick RA, McCall CO. Azathioprine in dermatology: the past, the present, and the future. J Am Acad Dermatol 2006; 55:369-89.
[2] Hadda V, Pandey BD, Gupta R. Azathioprine-induced pancytopenia. A serious complication. J Postgrad Med 2009; 55:139-40.
[3] Fraser JA, Weyand CM, Newman NJ, Biousse V. The treatment of giant cell arteritis. Rev Neurol Dis 2008; 5:140-52.
[4] Gisbert JP, Gomollon F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. Am J Gastroenterol 2008; 103:1783-800.
[5] Murugesan R, Vahab SA, Patra S, Rao R, Rao J, Rai P, et al. Thiopurine S-methyltransferase alleles, TPMT (*)2, (*)3B and (*)3C, and genotype frequencies in an Indian population. Exp Ther Med 2010; 1:121-7.