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Azathioprine Induced Pancytopenia In A Patient With Normal TPMT Levels

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Abstract

Azathioprine(AZP) has proven its efficacy and remains the mainstay of treatment after the confirmed diagnosis of Myasthenia Gravis. Inherent genetic multiformity in TPMT activity of different individuals has a great impact on AZA response in patients. TPMT remains the key enzyme in 6-MP metabolism and the deficiency in TPMT enzyme can lead to accumulation of 6-MP which further converts to cytotoxic 6-thioguanine nucleotide analogues, which can lead to bone marrow toxicity and myelosuppression. This case report indicates that there might be other genetic pathways involved in the metabolism of AZP as this patient developed pancytopenia despite the normal TPMT report which further improved after the withdrawal of AZP. Further investigation and close monitoring of AZP therapy with TPMT report in different individuals is still needed to prove this hypothesis.

Keywords: Azathioprine, Pancytopenia, TPMT, 6-mercaptopurine, Myasthenia Gravis

Introduction

Azathioprine is an antipurine agent that acts by getting converted to 6-mercaptopurine. Purine antagonists are effectively used as an antineoplastic agent but AZP has more prominent immunosuppressant action than antitumor. The AZP structure was synthesized to protect the sulfhydryl group of 6-MP from In vivo "methylation", but subsequent studies have shown that after an oral dose AZP is rapidly converted to 6-MP. The immunosuppressant action of azathioprine may be due to its selective uptake into immune cells and intracellular conversion of 6-MP, which then further transforms to inhibit de novo purine synthesis and damage DNA. [1] AZP primarily suppresses cell mediated immunity(CMI). It is used in autoimmune diseases like Rheumatoid Arthritis, ulcerative colitis, myasthenia gravis as well as in organ transplantation. Azathioprine undergoes metabolism and eliminate from the body by the enzyme TPMT, but the deficiency of TPMT enzyme can cause azathioprine toxicity, by suppressing bone marrow. The incidence of myelosuppression changes among different ethnic groups based on the TPMT polymorphism.[2] Leukopenia is the most common adverse drug reaction of azathioprine with an incidence of 28-50%. This case report will help the primary care physician as well as general physician to identify the adverse effects in patients who are on chronic AZP therapy and thus it should be considered as a signal generation to be aware and closely monitor TPMT levels before initiating the treatment with Azathioprine.[3]

The Case:

A 32 year old female patient presented with the complaints of difficulty in breathing, generalised weakness, difficulty in walking, difficulty in swallowing and chewing since one week and increased breathing difficulty since one day on 29th

april 2019. On examination the patient was conscious and oriented and the respiratory system revealed decreased air entry in the lower zone of both lungs. Patient's ANA(antinuclear antibodies) test was found negative, MUSK antibody test for myasthenia gravis was negative but AChR(Acetylcholine Receptor Antibodies) was found positive (24.9 nmol/L) and all levels above 0.40 is referred as positive according to the reference interval provided in the lab investigation report. With a positive AChR report and correlating with underlying symptoms, the patient was diagnosed with Myasthenia Gravis and was further admitted in the hospital for the next 15 days. During her 15 days hospital stay the patient was treated with tablet pyridostigmine 60mg TID,tablet prednisolone 30mg OD, tablet azathioprine 50mg BID, all being the mainstay of treatment along with standard of care including antiemetic, antacid, analgesics and multivitamins. After 5 days, the dose of azathioprine was increased to 50mg TID. After 15 days of hospital stay, the patient was clinically improved and feeling better and was discharged with tablet pyridostigmine 60mg TID, tablet azathioprine 50mg TID, and prednisolone 50mg OD. Patient periodically followed up with a neuro physician after every 3-4 months ensuring medication adherence and was also being analysed for myelosuppression by azathioprine at every followup by periodic CBC and dose of azathioprine was fixed 100mg BID. On 13/12/2021, after almost two years of initiation of medication, the patient came with complaints of pain over the right half of the head since four days which is moderate in intensity and with no recurrence of weakness in the last two years. Her vitals were stable and CBC with differential count, haematology report, biochemistry report,serum iron concentration and TPMT report were advised.

Parameters	Result	Normal range
COMPLETE BLOOD COUNT		
Haemoglobin	5.7	12.5-15 g/dl
Haematocrit	16.7	36-46 %
RBC count	1.40	3.8-4.8 million/mcL
MCV	119.7	83-101 fl
MCH	40.6	27-32 pg
MCHC	33.9	31.5-34.5 g/dl
WBC count (TLC)	2820	4000-10000 cells/mcL
Platelet count	49	150-410 thousands/mcL
DIFFERENTIAL COUNT		
Neutrophil	55	40-80 %

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Lymphocyte	40	20-40%
Eosinophil	02	1-6 %
Monocyte	03	2-10 %
Basophil	00	0-1 %
HAEMATOLOGY		
RBC morphology	Macrocytosis (++) Anisocytosis (++)	-
WBC morphology	Leukopenia	-
Platelets on smear	Moderate thrombocytopenia	-
Reticulocyte count	2.0	0.5-2.5%
IRON STUDIES		
Serum iron	272	50-170 mcg/dL
Serum UIBC	19.5	135-392 mcg/dL
Serum TIBC	292	250-425 mcg/dL
Transferrin saturation	93	14-50 %
TPMT genotype	*1/*1	Normal TPMT enzyme activity

Patient was treated by discontinuing azathioprine and was started with a granulocyte colony stimulating factor;filgrastim along with standard of care including iv antibiotics, antacids, antiemetics, iv fluids, multivitamins and oral folic acid.

Discussion:

AZP is a commonly used immunosuppressant in Myasthenia gravis and other autoimmune diseases. AZP-induced myelosuppression is an occasional complication. During metabolism, 6-MP converts to cytotoxic 6-thioguanine nucleotide analogues where AZP exerts its immunosuppressive effects. An alternative metabolic pathway of 6-MP is via xanthine oxidase which will form 6-thiouric acid which is non-toxic and can be cleared by the body. Another pathway is via thiopurine methyltransferase forming 6-methyl mercaptopurine which is also non-toxic. But in patients with TPMT deficiency, a large proportion of 6-MP converts to cytotoxic 6-thioguanine, without this enzyme the body cannot eliminate the drugs by metabolizing them into

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inactive products.[3] That can cause the accumulation of thiopurine drugs in the body for a longer period of time and leads to bone marrow suppression. Damaged bone marrow cannot produce enough red blood cells, white blood cells and platelets. Deficiency of hematopoietic cells can cause health issues like abnormal bleeding and an increased risk of life threatening infections. Individuals with TPMT deficiency are more prone to produce toxicity while on thiopurine drugs.[4][5][6]

Using the Naranjo Adverse Drug Reaction (ADR) Probability Scale, the likelihood of this patient's pancytopenia being caused by an ADR is probable(6).[7] The clinical manifestations and laboratory reports clearly indicates that this patient is suffering from severe pancytopenia .The TPMT genotype result detected *1/*1 that interprets a normal enzyme activity. Severe pancytopenia even with a normal TPMT report is the rare finding identified in this case.The risk of adverse reactions to thiopurines may be affected by additional genetic and non-genetic factors not evaluated by this test.High enzyme activity is found in approximately 86-97% of individuals.High dose of azathioprine or Low activity of TPMT leads to toxicity.[8] Patients may develop pancytopenia within 3weeks of exposure,although the exact time course of pancytopenia may be variable it depends on the coadministration of other therapies. Similarly it will take almost three to four weeks for the recovery after the discontinuation of azathioprine. There may be a continuous decrease in cell counts occur even after discontinue the azathioprine, That is due to the uncleared or persisted serum 6- mercaptopurine level.[9][10][11]Physicians should be aware about this and not misdiagnose as further cytopenia. Late onset myelosuppression has a more gradual onset and can therefore safely be detected by changes in blood counts. TPMT testing is the effective way of finding the probability of developing myelosuppression but due to high expense and limited practice it is not recommended normally. Frequent blood count monitoring is mostly preferred to avoid toxicity.[12][13]

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