Case Report

To err is…Drug? Patient? Doctor? Healthcare System?

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ABSTRACT

Medicine is a practicing art. This is because we evolve constantly with everyday learning. The core of the health care system is management of patients with pharmacological measures. However the role of the health care deliverers does not stop with prescribing drugs. It is of central importance to be aware of the potential side effects of the drug including the rarest of the complications. It is equally important to discuss with our patients the available choices, the risk - benefit ratio and counsel them accordingly regarding anticipated common and rare side effects. The patient must be repeatedly reinforced about the importance of periodic follow up with the doctor, need for regular laboratory monitoring and reporting of alarm signs without any delay. Thus patient education, awareness of drug characteristics and a detailed doctor prescription are central in avoiding as well as managing drug related adverse effects. Here we present a case series of 9 different patients presenting with varied drug related adverse effects.

Key words: Adverse drug reactions, Periodic Monitoring, Patient education, Warning signs, Physician role.

INTRODUCTION

The European Medicines Agency (EMA) defines an adverse drug reaction as "a response to a medicinal product which is noxious and unintended.[1] The US Food and Drug Administration (FDA) defines an adverse drug reaction as any untoward medical occurrence associated with the use of a drug in humans "for which there is a reasonable possibility that the drug caused the adverse event."[2] Most of the drug reactions usually go underreported. Doctor prescription, drug characteristics and patient education are the three vertices of the adverse drug management triangle.

Drug reactions could be highly characteristic or nonspecific.[3] They could be dose, frequency or time dependent, occurring either almost right away or much later. Polypharmacy is a clear culprit in the occurrence of adverse drug reactions.

Patient factors like age, gender, creatinine clearance, body weight and fat distribution, race, ethnicity, genetic susceptibility, smoking and alcoholism are well known factors contributing to adverse drug reactions.[4] Patient education of drug intake, timing with other drugs, other co-morbidities, alertness in early recognition and reporting of warning signs are also of paramount importance.

A physician should be insightful in drug prescription fully taking into consideration previous drug histories and other simultaneous drugs the patient is on. It is wise to restrain hurry while diagnosing the disease or prescription even on a crowded day practice. It is prudent to refer the patient when required or have a close follow up while in doubt.

CASE REPORT

Case 1

A 58 yr old male patient presented with history of fever, loose stools and abdominal discomfort for 1 week. Patient was diagnosed

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with Myasthenia gravis 3 months ago elsewhere and started on immunosuppressants with oral Prednisolone 5mg once daily, Azathioprine 50mg once daily and Pyridostigmine 60mg thrice daily.

His examination was normal except for right eye ptosis. His initial blood counts showed pancytopenia as shown in Table 1. Bone marrow biopsy was suggestive of myelosuppression. With the diagnosis of drug induced pancytopenia, azathioprine was withheld and he was started on broad spectrum antibiotics and antifungal agents. Patient was given an injection of Granulocyte-Colony Stimulating Factor (G-CSF), following which his counts steadily improved. 2 weeks later patient reported with normal blood counts and patient was put on Mycophenolate mofetil along with pyridostigmine and steroids. Currently the patient's myasthenic symptom has improved and is maintained on oral prednisolone 10 mg once daily.

Case 2

27 year old female was admitted with history of fever for 3 days. Patient was evaluated elsewhere for a right sided neck swelling 1 month ago. A Computed Tomography (CT) Angiogram of the chest had shown Aortoarteritis changes suggestive of vasculitis for which she was treated with oral Azathioprine 50 mg once daily and oral Methotrexate 10 mg weekly.

On admission she was pale and tachypnoeoic tachypnoeic with gingival petechial petechiae. Her blood counts showed severe pancytopenia (Table 1). With a clinical diagnosis of drug induced bone marrow suppression, patient was put on strict barrier nursing with empirical antibiotics and antifungal agents. Patient required supportive transfusion with packed red cells, platelets and G - CSF in view of profound pancytopenia. However a week later, patient developed persistent dry cough, left peri orbital hematoma, hoarse voice, hypotension and stridor. A chest imaging and tracheal aspirate were suggestive of Aspergillus. Patient was put on mechanical ventilation and high end antibiotics and antifungal agents but eventually succumbed to refractory septic shock.

Case 3

58 year old female patient was admitted with history of recurrent nasal and gum bleeding for 1 month. Patient was diagnosed with *Pemphigus vulgaris* and had been taking Methotrexate 7.5mg weekly once for 10 years.

On examination, patient was pale and had non pruritic, non-blanchable multiple hyper pigmented maculae all through the body. Initial investigations as displayed in Table 2 showed pancytopenia and subsequently a bone marrow biopsy was suggestive of myeloid suppression with no atypical cells. Patient was started on intravenous antibiotics and transfused with packed red cells and platelets. Further the skin lesions were suggestive of psoriasis and patient was managed with antihistaminic drugs and topical applications. A month later patient reported with normal counts and is doing well on topical steroids and moisturizers.

Table 1: Showing the bicytopenia pattern in case 1 and subsequent improvement; case 2 showing persistent pancytopenia.

		CASE 1				CASE 2				
Lab parameter	Reference range	Day 1	After G-CSF	2 weeks later	1 year later	Day 1	Day 3	Day 5	Day 9	Day 15
Hemoglobin	13 - 17g/dL	10.2	10.9	14.8	9.6	3.8	7.5	9.5	9	6.3
Total white blood count (WBC)	4-10x10^3/uL	0.8	6.8	6.6	8.4	0.7	1.3	1.7	2.2	0.6
Platelets	150-400x10^3/uL	261	556	247	212	22	9	3	10	11

Table 2: Showing the drug induced pancytopenia in case 3, 4 and 5 with subsequent improvement.

Lab parameter	CASE 3				CASE 4					CASE 5				
	Day 1	Day 5	A month later	A year later	Day 1	Day 3	Day 6	2 weeks later	2 months later	6 months prior to treatment	Day 1	Day 2	2 days after G-CSF	1 Month later
Hemoglobin	7.1	8.2	8.4	10.0	8.2	9	10.1	8.0	13.2	8.5	4.4	5.3	6.5	9.9
White blood count	2.1	3.9	14.7	6.8	0.3	1.9	4.3	10.5	6.2	8.5	3.1	1.8	8.0	6.7
Platelets	4	86	187	211	30	37	65	617	242	246	75	53	117	153

Case 4

68 year old male patient was admitted with complaints of fever, productive cough and breathlessness for 2 days. Patient was a known case of Rheumatoid arthritis on oral Methotrexate 5 mg weekly for 8 years.

On admission, patient was severely dyspnoeic and tachypnoeic, had bilateral lung crepitations with Varicella zoster skin lesions. His initial investigations showed pancytopenia (Table 2). Patient was treated with empirical antibiotics, antifungal and antiviral drugs. He was supported with blood products transfusion and G-CSF. His tracheal and urine cultures revealed multidrug resistant *Klebsiella pneumonia*. Patient had a tumultuous hospital stay where he required reintubation after weaning owing to excessive oropharyngeal secretions which was further complicated by an episode of atrial fibrillation reverted by cardio version. After aggressive management with sensitive antibiotics and ventilator support, patient improved symptomatically and he was able to mobilize around in wheel chair. Patient was discharged with Hydroxychloroquine tablet 200 mg once daily and reported on follow up with improved counts and no active inflammatory signs.

Case 5

51 year old female patient was admitted with history of generalized fatigability, exertional dyspnoea and swelling of legs for 10 days. She was diagnosed with Rheumatoid arthritis for the last 2 years. Initially the patient had taken native medication for her joint pain and then subsequently started elsewhere on weekly Methotrexate dose of 5 mg, Leflunomide 10 mg daily and 5 mg once daily prednisolone for the last 6 months. On examination, the patient was pale, had glossitis, bilateral pitting pedal edema and crepitations in the lungs. Initial investigations (Table 2) showed pancytopenia. On the suspicion of drug induced pancytopenia, methotrexate and leflunomide were withheld. Patient was started on broad spectrum antibiotics and antifungal agents with strict barrier nursing. Bone marrow biopsy showed hypo cellular marrow with no atypical cells. The patient was administered one dose of G-CSF and 2 units packed red cells were transfused. Her blood counts gradually started improving and patient was discharged with low dose oral prednisolone and is maintained on the same on follow up.

Case 6

59 year old female patient presented with breathlessness, decreased urine output, swelling of legs for the last 2 days. Patient had started developing facial puffiness a month ago for which she was suggested thyroid function tests elsewhere. Her Thyroid Stimulating Hormone (TSH) levels were 6 microIU/ml and patient was started directly on 100 micrograms (mcg) Levothyroxine.

On examination, the patient was tachypnoeic, had anasarca and extensive bilateral lung crepitation's. Her cardiac markers were elevated and an echocardiogram showed mild pericardial effusion with preserved ejection fraction and cardiomegaly. A diagnosis of levothyroxine induced heart failure was arrived at and patient was treated with noninvasive ventilation, diuretics and her Levothyroxine dose was brought down to 50 micrograms/day. Patient gradually improved and was discharged with 50 mcg of Levothyroxine. On follow up her dose was gradually increased by 12.5 mcg and patient is doing well on tab. Levothyroxine 75 micrograms per day.

Case 7

A 29 yr old female patient with no known previous co morbidities came with complaints of generalized swelling of body, decreased urine output and orthopnea for 1 week. Patient was apparently normal 3 months back when she started having hair fall, mild facial puffiness, dyspnea on exertion and dryness of skin but was able to attend to her household work. She had consulted elsewhere, her TSH levels were 5.3 micro IU/ml and the patient was started on tablet Levothyroxine 100 mcg following which her breathlessness exaggerated.

On examination, the patient was dyspnoeic, tachypnoeic, had anasarca and oral ulcers with lung crepitations. A clinical diagnosis of a volume overload status due to Levothyroxine induced heart failure with underlying connective tissue disease was arrived at and Levothyroxine was stopped. Initial investigations showed mild neutrophilic leukocytosis, elevated ESR with severe nephrotic range proteinuria as Table 3. Her Antinuclear Antibody (ANA) pattern was 3+ with hypocomplementemia. An echocardiogram showed grade 1 diastolic dysfunction. Patient was started on diuretics, noninvasive ventilation, intravenous Methylprednisolone 250 mg injection (3 doses) and albumin infusion. Patient subsequently improved; a week later patient developed sudden breathlessness, a CT pulmonary angiogram showed a left sub segmental pulmonary thromboembolism and antiphospholipid antibodies were also positive. Patient was administered anticoagulation and improved well. Patient was discharged a week later with oral prednisolone 40 mg once daily, oral anticoagulants and Hydroxychloroquine (HCQ). A year later patient is doing well on follow up with normalized disease markers and is on oral Prednisolone 5 mg once daily and Mycophenolate mofetil 500 mg twice daily.

Case 8

45 yr old female patient was admitted with history of fever and cough for 1 week. She was a known case of endometrial carcinoma on chemotherapy. She had undergone her 5th cycle with Paclitaxel a week ago. Patient also had underlying diabetes mellitus and chronic kidney disease, which were conservatively managed.

On examination, the patient was pale, tachypnoeic and febrile with bilateral lung crepitations. Investigations showed severe metabolic acidosis, profound pancytopenia, high procalcitonin and deranged renal functions as summarized in Table 4. Chest x-ray showed left lower lobe pneumonia. A diagnosis of febrile neutropenic sepsis was made and patient was put on aseptic precautions and barrier nursing. She required aggressive management with Granulocyte Colony Stimulating Factor, antibiotics, antifungals, antivirals, antipyretics, bicarbonate infusion and other supportive measures. Patient gradually improved and was discharged with oral antibiotics and had normalized blood counts on follow up.

Case 9

50 yr old male presented with progressive difficulty in walking over the last 8 months. He was diagnosed with retroviral disease 8 years ago and was on Tenofovir, Lamivudine and Ritonavir boosted Atazanavir for the last 4 years.

On examination, the patient was emaciated and decreased range of movements in the lower limbs due to pain. Initial investigations showed hypokalemia, hypophosphatemia with significant metabolic acidosis. Urine showed albuminuria (3+) and glycosuria (3+). His liver functions also showed deranged alkaline phosphatase levels and vitamin D levels were normal (Table 5). Subsequently an X-Ray and Computed tomography of the hips showed bilateral fracture neck of femur. Hence a diagnosis of Tenofovir induced proximal renal tubular acidosis and bone toxicity was arrived at and tenofovir was promptly withheld. Patient was managed with intravenous fluids, potassium and bicarbonate supplementation with thiazide diuretics. Bilateral open reduction with internal fixation was planned, however patient opted conservative management. His HIV viral load and CD4 counts were in the improving trend compared to previous year values. After hypersensitivity testing, patient was started on Abacavir / Lamivudine and Doultegravir regimen and was discharged with oral potassium and bicarbonate supplements. Patient reported to follow up with normal electrolytes and is attending to activities of daily living.

DISCUSSION

Drug related adverse effects are thus not an uncommon entity. Rather it is grossly underreported. This case series has observed drug reactions in 9 patients who were admitted in PSG Institute of Medical sciences and

Table 3: Showing the thyroid pattern at admission, nephrotic range proteinuria and hypocomplementemia in case 7.

Lab parameter	At admission	1 month after discharge	A year later	Reference range
T3 (Serum)	0.37	1.06		0.846 - 2.02 ng/mL
FT4 (Serum)	0.98	1.12		0.932 - 1.71 ng/dL
TSH (Serum)	0.484	1.68		0.27 - 4.2 microIU/ml
FT3 (Serum)	0.64	2.92		2-4.4 Pg/ml
Urine Protein Creatinine Ratio	27.33	10.108	0.070	
Serum Creatinine	0.83			0.66 - 1.09 mg/dL
Serum albumin	0.7 g/dl	1.5	3.4	3.4 - 4.8 g/dL
Complement 3c level	28.42mg/dl	79	102	90 - 180 mg/dl
Complement 4 level	10mg/dl	14	16	10 - 40 mg/dl

Table 4: Showing the pancytopenia and subsequent improvement with treatment in case 8.

Lab parameter	Day of admission	After 1st dose G-CSF	After 3rd dose G-CSF	Day of discharge	10 days after discharge	Reference Range
Creatinine mg/dl	3.6	3.4		2.83	2.6	0.66-1.09 mg/dl
Hemoglobin g/dL	6.7	6.4	5.5	7.6	9.0	13 - 17g/dL
Total WBC 10^3/microL	0.2	0.5	5.1	10.1	5.7	4-10x10^3/uL
Absolute Neutrophil Count 10^3/uL	0.0	0.2	4.7	9.2	4.5	2 - 7x10^3/uL
Plateletsx10^3/uL	64	63	61	82	324	150-400x10^3/uL

Table 5: Showing the hypokalemia and metabolic acidosis pattern in case 9.

Lab parameter	Day 1 of admission	Day 3	Day 5	Month after discharge	Reference range
Serum Creatinine	1.75	1.26	1.6	1.43	0.8 - 1.25 mg/dl
pH	7.230	7.342	7.334	7.33	7.35-7.45
Serum Potassium	2.45	4.6	3.0	3.66	3.5 - 5.0mEq/L
Serum bicarbonate	12.5	15.9	17	21.6	22 - 30mEq/L
Serum ionised Calcium	1.202			1.2	1.1-1.3m mol/L
Serum Phosphous		2.1			2.7-4.5 mg/dl
Serum Alkaline phosphatase	459				40 – 129 U/L

Research, a tertiary care hospital in Coimbatore, Tamil Nadu. They were either referred from their primary care physician and/or admitted in our emergency department with severe drug related adverse events. The discussed 9 patients were on different class of drugs for their respective diagnosis prescribed elsewhere and presented to us with a variety of adverse effects requiring hospitalization or developing grave complications. Fortunately 8 of them recovered with prompt diagnosis and withdrawal of the offending drug.

Azathioprine is an imidazolyl derivative of mercaptopurine which acts by blocking the pathway for purine synthesis. The 6-thioguanine nucleotide metabolites appear to mediate the majority of azathioprine's immunosuppressive and toxic effects. Azathioprine, though a well-established immunosuppressive drug for myasthenia showing improvement in 70-90% patients has its share of serious complications.

Of grave concern is haematological toxicity. Dose-related immediate or delayed severe hematologic toxicities in the form of leucopenia, thrombocytopenia or pancytopenia may occur. Panda BK *et al.* have reported a case of severe pancytopenia in a patient of myasthenia gravis following azathioprine.[5] Other side effect profile includes gastrointestinal disturbances, hepatotoxicity and carcinogenic potential. Therefore it is important to periodically monitor blood counts and educate the patient about the need for the same.

In our case 1, the patient was not aware of the potential complication of his drugs, thereby delayed presenting to the hospital until he had profound leucopenia. With a proper patient education, early diagnosis can be arrived at and prompt action can avoid grave consequences. Case 2 patient was co-prescribed with azathioprine and methotrexate - both contributing to her profound pancytopenia. Patient had a tumultuous hospital course warranting intensive care admission, developed grave fungal and bacterial infections and succumbed to the same. Therefore it is crucial to carefully evaluate and closely follow up patients while co prescribing 2 potential hematotoxic drugs.

Thiopurine methyltransferase (TPMT) genotyping or phenotyping and nudix hydrolase 15 (nucleotide diphosphate [NUDT15]) genotyping may help to identify patients who are at an increased risk for developing azathioprine related hematological toxicity.[6] Once identified, patients may require dose reduction, interruption or selection of an alternate agent altogether.

Methotrexate being a folate antimetabolite inhibits dihydrofolate reductase, thereby hampering purine and thymidylic acid synthesis. DNA synthesis, repair and cellular replication are thus hindered as methotrexate targets actively proliferative tissues more and is therefore used in a number of conditions like rheumatoid arthritis, psoriasis as well as certain malignancies.

Thrombocytopenia (3% to 10%), leukopenia (1% to 3%), pancytopenia (1% to 3%), agranulocytosis, anemia, aplastic anemia, bone marrow suppression are noted hematological adverse effects of methotrexate. That is why it is pertinent to closely monitor the complete blood counts prior to initiation, weekly in the first month of initiation, every 2 to 4 weeks in the first few months and monthly thereafter. In a study of 46 patients on methotrexate in Lucknow, India, it was noted that initial WBC count was a predictor for development of pancytopenia later.[7] Patients with renal insufficiency or older age will require frequent monitoring. Case 3 (a female patient) and case 4 (older age group) had been taking only low dose methotrexate in weekly schedule for years, yet presented with pancytopenia revealing the fact that even low dose methotrexate can cause pancytopenia as a delayed presentation and periodic monitoring is indispensable. These findings are similar to a case series report on methotrexate where pancytopenia was encountered as a later manifestation[8] and another case report which observed low dose methotrexate causing

pancytopenia.[9] Once hematotoxicity is encountered, the drug is withheld, serum methotrexate levels are monitored and leucovorin rescue dosing is done to combat methotrexate effects. Granulocyte Colony stimulating factors will also be required where the patient has persistent pancytopenia. Hepatotoxicity and lung toxicity also require close attention and a baseline work up for the above is mandatory before starting methotrexate.

Leflunomide is an immunomodulatory agent that inhibits pyrimidine synthesis, resulting in its antiproliferative and anti-inflammatory effects. It acts by inhibiting dihydroorotate dehydrogenase and is converted to the active metabolite A771726 on administration.[10] Usually used in rheumatoid arthritis and systemic lupus erythematous. In November 2003, FDA issued a drug safety alert update on leflunomide, warning of rare post marketing reports of bone marrow suppression and sepsis. Though rare (incidence of 1 in 3698 patients) the incidence of pancytopenia is potentiated by concomitant administration of other myelotoxic agents as in case 5 where the patient was on both methotrexate and leflunomide. And myelosuppression can persist even after discontinuing the drug owing to its long half-life. A number of case reports reinforce the fact that hematological toxicities of methotrexate and leflunomide combination therapy are deleteriously additive.[11]

Levothyroxine (T_4) is a synthetic form of thyroxin, which is an endocrine hormone secreted by the thyroid gland. T_4 is converted to its active metabolite, L-triiodothyronine (T_3). Thyroid hormones (T_4 and T_3) then bind to thyroid receptor proteins in the cell nucleus and exhibit their metabolic actions through control of DNA transcription and protein synthesis.

While a decision to start a patient on levothyroxine is arrived at, certain characteristics should be carefully checked. These include patient's weight, lean body mass, etiology of hypothyroidism, pregnancy, age and cardiac disease. Thyroid hormone can be started at anticipated full replacement doses in individuals, who are young and otherwise healthy in most situations, a starting levothyroxine dose of 50-75 μg/day (1.6 μg/kg/day) will suffice. In patients with coronary heart disease, initial dose should be 12.5 to 50 μg/day.[12] Aggressive replacement of thyroid hormone in initial higher doses may worsen cardiac function in patients with existing cardiac disease. That is why it is imperative to start these patients on smaller doses and then titrate in small increments after no less than 4-6 weeks. Achieving a target TSH level at times may take several months owing to delayed preadaptation of the hypothalamic-pituitary axis. Therefore in patients receiving treatment with Levothyroxine, dosing changes should be made every 6-8 weeks only in usual scenarios.

In our case 6, 59 yr old woman was forth right put on high dose levothyroxine 100 micrograms for a TSH value of 6 microIU/ml exacerbating her heart failure. In case 7, though the patient had an underlying connective tissue disease, she was able to attend to her activities of daily living. However challenging her with levothyroxine 100 micrograms for a TSH value of 5.13 microIU/ml clearly exaggerated her symptoms precipitating her cardiac failure resulting in emergency presentation and subsequent prolonged hospitalization, which could have been avoided.

Treatment with levothyroxine in patients with heart failure is associated with a higher risk for all-cause mortality, cardiovascular death and major adverse cardiac events according to findings published in The Journal of Clinical Endocrinology and Metabolism.[13] These events are attributed to the low T3 syndrome. When hypothyroidism is treated with levothyroxine, there is often a relatively high thyroxin/T3 ratio in serum with relatively low liothyronine levels in blood, which could further exacerbate the T3-deficient state in patients with chronic heart failure

Paclitaxel is a natural taxane promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules and inhibits their disassembly. These actions ultimately halt cell replication thereby modulating the desired immune response. Paclitaxel finds usage in a variety of conditions notably breast, ovarian malignancies, lung cancer and Kaposi sarcoma. Our index patient case 8 was on paclitaxel for endometrial carcinoma. The hematological adverse effects include neutropenia (78% to 98%), leukopenia (grade 4: 17%), anemia (47% to 90%), thrombocytopenia (4% to 20%). It is therefore crucial to regularly monitor the complete and differential blood counts of the patient while on chemotherapy.

Chemotherapeutic agents do exaggerate the immune compromised state of cancer affected patients. Usually the magnitude of the neutrophil mediated component of the inflammatory response may be muted in neutropenic patients with fever sometimes being the only sign of infection. It is critical to recognize neutropenic fever early and to initiate empiric therapy promptly in order to avoid progression to a sepsis syndrome and possibly death. Neutropenic patients have the risk of developing a neutropenic fever syndrome, risk of resultant medical complications as well as risk of non-response to empiric antibiotic treatment.[14]

Certain risk factors are predictive of the development of a neutropenic fever syndrome. Patient-related predictors include age> 65 yrs, female sex, high body surface area and poor nutritional status. Disease-related predictors include elevated lactate dehydrogenase, advanced malignancy staging and myelophthisis. Treatment-related predictors of neutropenic fever include administration of high dose chemotherapy regimens and failure to administer hematopoietic growth factor support to patients receiving high-risk regimens. High risk patients are those who have other co morbidities, significant hepatic or renal impairment or those who are expected to be severely neutropenic (absolute neutrophil count [ANC] <500 cells/microL) for >7 days. The index patient case 8 was a female patient with diabetes mellitus and chronic kidney disease enhancing her risk of pancytopenia.

A number of validated tools are used to calculate the risk index for measuring the risk for neutropenic fever–related medical complications and must be put to effective use wherever possible in tertiary centres.[15] In a research article that investigated the capability of genetic variation in drug metabolizing enzymes and transporters (DMET platform) to predict haematological toxicity, the single nucleotide polymorphism SNP rs 9285726 in MAT1A (methionine adenosyl transferees) and SNP rs 776173 in CYP39A1 were found to be associated with neutropenia. These are potential areas of research in predicting paclitaxel induced hematologoxical toxicity and in picking up individual patients who are at more risk.[16]

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor. It interferes with the HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication exhibiting its action via active tenofovir diphosphate. Nephrotoxicity is a known and established side effect of tenofovir. One study reported that the incidence rate of moderate or severe renal insufficiency caused by tenofovir was 29.2 and 2.2 cases per 1000 person-year respectively. Apart from this tenofovir can also cause interstitial nephritis, lactic acidosis, nephrogenic diabetes insipidus and rhabdomyolysis and decreased bone mineral density.[17]

Tenofovir can rarely cause Fanconi syndrome.[18] It is a proximal tubulopathy causing impaired reabsorption of glucose, aminoacids, bicarbonate and phosphate resulting in their excretion. The presentation of fanconi syndrome can be quite delayed also in a patient on tenofovir.[19] Therefore drug related adverse effect should be considered in any patient presenting with renal tubular acidosis type 2 while on tenofovir regardless of the duration of drug exposure.

Our case 9 patient also developed toxicities 4 years after tenofovir exposure and developed Fanconi's syndrome as well as bone toxicity which is quite rare.[20] The index patient however improved remarkably after stopping Tenofovir and with calcium and phosphate supplementation. This finding is similar to a study from Christian Medical College, South India where the incidence of tenofovir induced renal tubular toxicity has been observed as quite rare (3.6%) and the average latency period between tenofovir exposure and nephrotoxicity was prolonged (42 months).[21] The study suggests that patients on tenofovir should be monitored serially and periodically for proteinuria, creatinine clearance rather than creatinine values, hypophosphatemia and alkaline phosphate levels. Tenofovir alafenamide is the pro-drug of TDF which achieves higher intracellular concentrations rather than plasma concentrations at low dose, thereby resulting in lower toxicities and similar efficacy.

CONCLUSION

Thus it is important to choose and prescribe drugs and their dosage carefully. It is fundamental for the treating doctor to be aware of drug combination/interactions leading to profound side effects. Patient education and awareness of drug related side effects is core in management and helps in averting serious side effects earlier and thereby avoiding unnecessary/prolonged hospitalization and related complications. As a physician it is pertinent to constantly update and learn from errors whether of one's self or others. After all learning and unlearning is part of the continuing medical education process.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ANA: Antinuclear antibody; **HCQ:** Hydroxychloroquine; **TSH:** Thyroid stimulating hormone; **CSF:** Colony stimulating factor; **TPMT:** Thiopurine methyltransferase; **NUDIT:** 15 nucleotide diphosphate 15; **ANC**: Absolute neutrophil count; **TDF:** Tenofovir disoproxil fumarate.

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