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Case Report

Reversible Myelofibrosis: Physicians Enigma, Nightmare, and Delight - A Rare Case Report

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ABSTRACT

Myelofibrosis is a rare haematological disorder with grave prognosis inflicting a toll on both Physician and Patient alike. However though rare, there is a small subgroup of Reversible Myelofibrosis which renders a great delight for both physician and patient. Here with we present one such case of Reversible Myelofibrosis a rare presentation due to a rare cause of Leflunomide intake, which has been rarely quoted in international literature. Our case gives the definitive conclusion that there is an absolute necessity for Initial Bone marrow analysis and also Repeat Bone marrow analysis though invasive to confirm the reversibility of myelofibrosis secondary to leflunomide. Thus our case is an epitome highlighting the Dilemma, Enigma, Nightmare, and Delight serially unravelling.

KEY WORDS: Myelofibrosis, Reversible Myelofibrosis, Bone marrow analysis, Repeat Bone marrow analysis, Leflunomide

INTRODUCTION

Myelofibrosis is a rare Haematological disorder affecting approximately 1 in 500000 people worldwide and being grouped in to Primary and Secondary Myelofibrosis.

Primary Myelofibrosis is characterized by fibrosis of Bone Marrow, Splenomegaly, Leucoerythroblastic blood picture with Tear drop poikilocytosis. Secondary Myelofibrosis can also occur as a secondary process following Other Myeloproliferative disorders (e.g.- Polycythemia vera, Essential thrombocytosis), Collagen vascular diseases (e.g.- SLE), Chronic infections(Eg- TB, HIV). The median survival among patients with Myelofibrosis from time of diagnosis is approximately five years [1] thus posing a nightmare for both physician and patient alike, while Reversible Myelofibrosis deliver delight and solace for both.

Here with we report a case of Reversible Myelofibrosis secondary to Leflunomide (a rare case and rare presentation) which is not evident in the published literature.

CASE REPORT

A 44 year old male working as a hotel manager, presented to us with history of fever of 20 days duration associated with generalized erythematous, pruritic, maculopapular skin eruption of 15 days duration. There was also history of jaundice of 8 days duration. There was no history of abdominal pain or distension, vomiting, loose stools, cough, bleeding diathesis. His past history was significant for short duration polyarthralgia for which he had been treated with medications daily for one month prior to onset of the present complaints after which he switched over to other medications. Details of the medications was not available at the time of admission. There was no history of alcohol consumption. There was no history of exposure to sexually transmitted diseases.

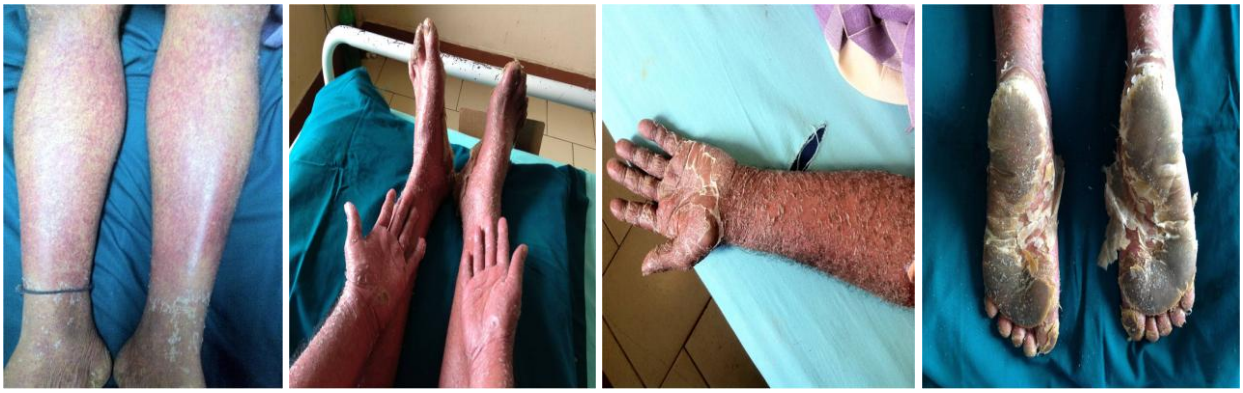

FIG 1-4: Erythematous scaly Skin lesions suggestive of Erythroderma.

On examination, patient was conscious and oriented. Vitals were stable and he was deeply icteric. There was no feature of hepatic encephalopathy. He had generalized erythematous, scaly lesion all over the body including face and scalp, which was diagnosed as erythroderma by the dermatologist (Fig1-4). Oral cavity showed superficial ulcerations. Systemic examination was within normal limits. Blood investigations revealed anaemia with haemoglobin of 9.9g/dl, Total count of 10,100cells/cumm, Platelet count of 1,45,000cells/cumm and ESR of 30mm/hr..Renal function was within normal limits with urea of 39mg/dl & creatinine 1.23mg/dl. LFT was suggestive of hepatitis with total bilirubin of 20.2 mg/dl , direct bilirubin of 14.7 mg/dl, AST of 782 IU, ALT 685 IU and ALP of 304 IU(Table 1).Peripheral smear was suggestive of leukoerythroblastic anemia with mean corpuscular volume(MCV)of 83.6. His blood was negative for viral markers for Hepatitis viruses and malaria parasite. ANA was negative. Ultrasound abdomen showed splenomegaly. A provisional diagnosis of drug induced hepatitis with erythroderma was made. Patient was started on meropenem and supportive therapy. A skin biopsy was taken from abdomen and forearm at the site of lesion and patient was started on 40 mg of oral steroids awaiting biopsy reports.

On day 5 of admission patient showed significant improvement in his liver function, however there was a fall in his hemoglobin to 8.9g%, total count to 3400 cells/cumm and platelet count to 42000cells/cumm and peripheral smear showed pancytopenia. He was transfused five units of platlets and two units of packed cells. Serial recordings of blood counts continued to show pancytopenia while Liver

function test showed gradual improvement (Table 2). A bone marrow biopsy and aspiration was planned and performed. Aspiration was unsuccessful in view of a dry tap. The biopsy was sent for histopathological examination. The biopsy was suggestive of myelofibrosis (Fig 5,6). Skin biopsy was suggestive of leucocytoclastic vasculitis. He was continued on antibiotics, oral steroids, iron and vitamin supplements. In the meantime meticulous history retaken identified Leflunamide (taken for arthralgia) as the culprit agent responsible for the clinical senerio.

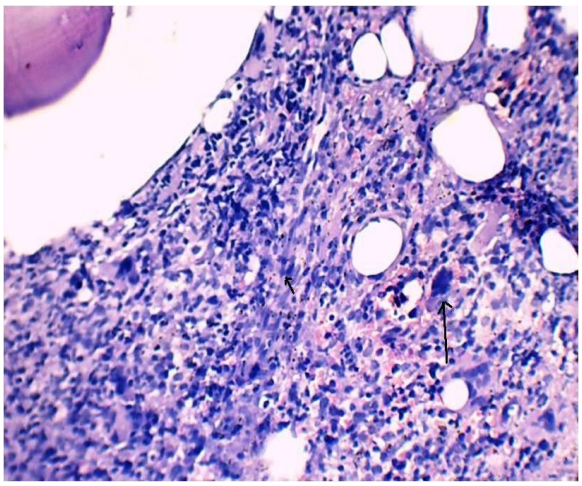

FIG 5: Low power view showing hyperplastic marrow with absolute increase in dysplastic megakaryocytes (big arrow) and marrow fibrosis (small arrow) (H & E Stain X10x).

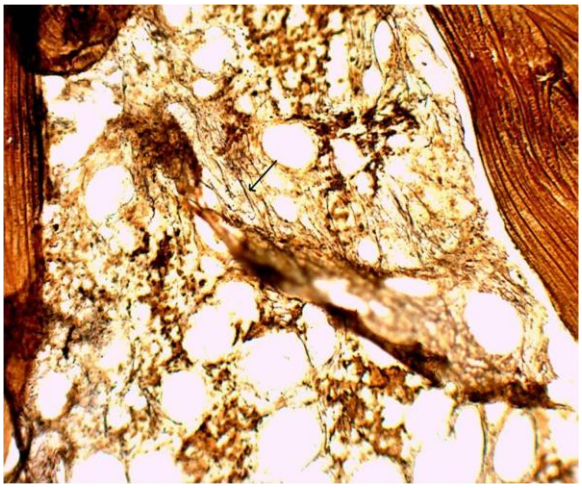

FIG 6: Reticulin stain of Bone marrow showing grade 2 increase in reticulin fibres (arrow)(reticulin stain X10x).

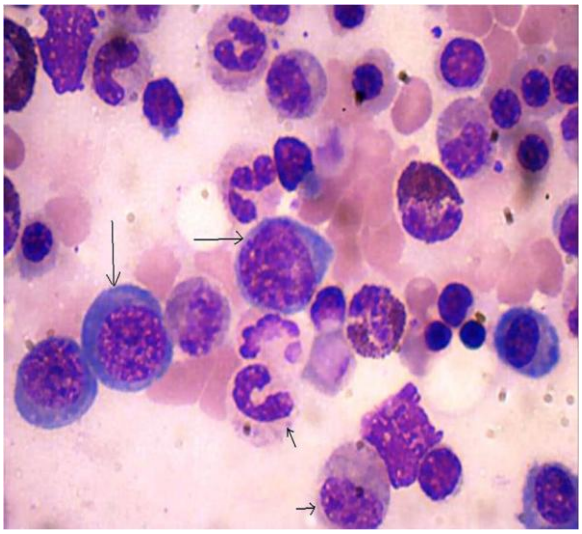

FIG 7: Repeat marrow aspirate smear showing many megaloblasts (big arrow) having large nuclei with open sieve like chromatin and dense inky blue cytoplasm with some giant myelocytes and band forms(small arrow) which are features consistent with megaloblastic anaemia.(Giemsa stain X100x).

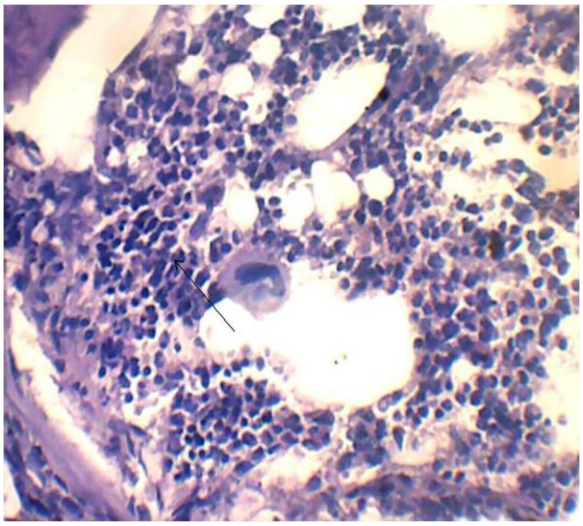

FIG 8: Repeat marrow biopsy microphotograph displaying erythroid hyperplasia (big arrow) with no evidence of any fibrosis. (H & E Stain X45x).

On day 17 of admissions patient was symptomatically better, skin lesions had subsided and were healing. Total counts and platelet count was within normal limits (Table 2). There was significant improvement in the liver function test. Patient was discharged on 20 mg of oral steroids, iron supplements and vitamin supplements.

Table 1: Baseline investigations of patient.

Investigations	On admission
Hb(mg/dl)	9.9
Total count(cells/cumm)	10100
Differential count	N-77,L-15,E-7
ESR(mm/min)	30
platelet(cells/cumm)	1,45000
urea(mg/dl)	39
creatinine(mg/dl)	1.23
S . sodium(mmol/L)	123
S .potassium(mmol/L)	4.1
RBS(mg/dl)	92
TP – Total proteins	7.4
Albumin	2.8
globulin	4.6
A:G	0.6
TB- Total bilirubin	20.2
DB-Direct bilirubin	14.7
IB-Indirect bilirubin	7.6
SGOT	782
SGPT	685
ALP	304

Table 2: Serial blood parameters.

Investigations	Day 5	Day 8	Day 17	2 months
Hb	8.9	7.9	11.5	12.8
Total count	3400	2500	7500	12300
Differential count	N36L53E11	N12L86E2		N68,L30,E2
platelet	42000	37000	1,68,000	3,38,000
urea		53		31
creatinine		0.75		0.7
TP	6.5	6.6	7.4	6.9
Albumin	2.6	3	3.2	3.3
globulin	3.9	3.6	4.2	3.6
A:G	0.6	0.8	0.7	0.9
TB	12.2	11.1	4.5	1.5
DB	10	8.6	3.5	0.7
IB	2.2	2.5	1	0.8
SGOT	229	138	57	17
SGPT	288	286	119	28
ALP	182	172	164	165

Patient was reviewed after 2 months in medicine OPD with blood investigations. His hemoglobin was 12.8 mg/dl, total counts 12300 cells/cumm and platlets were 3,38,000 cells/cumm and liver function tests were within normal limits (Table 2). He was admitted and a repeat bone marrow aspiration and biopsy was done. Aspiration was suggestive of megaloblastic change and bone biopsy displayed erythroid hyperplasia with no evidence of any fibrosis (Fig 7,8). Patient was discharged with methylcobalamine, folic acid supplements and reassurance.

DISCUSSION

The highlight of the present case is that our patient presented with prolonged pyrexia of 20 days along with jaundice, erythrodermal skin lesions, & pancytopenia which was preceded by arthralgia and intake of Leflunamide for a period of one month. Investigations including Bone marrow study confirmed Myelofibrosis and as all other major causes of Myelofibrosis being ruled out, leaving with the diagnosis of Leflunamide induced Myelofibrosis.

Leflunomide is a novel immunomodulating drug which is of interest for the treatment of the chronic inflammatory condition and has been included as a recent DMARD in the treatment of arthritis. It is a pyrimidine synthesis inhibitor which acts on mitochondrial enzyme dihydroorotate dehydrogenase and prevents the expansion of activated lymphocytes by interfering with their cell cycle progression. However this drug has been associated with a number of side effects some of which are life threatening . There is emerging evidence of a likelihood of pancytopenia, pneumonitis, and hepatotoxicity occurring with leflunomide which increase when it is is prescribed with methotrexate. Leflunomide induced hepatitis and skin manifestations

have been commonly reported while myelofibrosis has not been demonstrated with leflunomide in previous studies. [2,3] Pancytopenia is rare and morphological study of the marrow associated with this drug has been less reported in world literature. [4,5] A study conducted by FDA has shown that in 7930 people who reported to have side effects when taking leflunomide, only 77(0.97%) people were found to have pancytopenia. The relationship between appearance of pancytopenia and initiation of Leflunomide treatment has not been demonstrated.

There is absolutely no data available as on today with respect to (a) Time on Leflunomide when people have Myelofibrosis, (b) Gender of people who have Myelofibrosis when taking Leflunomide, (c) Age of people who have Myelofibrosis when taking Leflunomide, (d) Severity of Myelofibrosis when taking Leflunomide, and (e) How people recovered from Myelofibrosis. This is mainly due to extreme rarity of the condition and absence of Bone marrow studies in such cases.

However our case is unique as reversal of Myelofibrosis confirmed by a repeat Bone marrow study gives a ray of hope to the patient that a single bone marrow finding of myelofibrosis is not the end of the road for the patient.

CONCLUSIONS

Our case highlights the Enigma, Nightmare components of Myelofibrosis and final Delight after a repeat Bone marrow study. From the present study we conclude that-

Physicians should consider Myelofibrosis secondary to Leflunomide as a cause of Pancytopenia even though it is rare and advocate repeat Bone marrow analysis though invasive to establish the reversibility.

Repeat Bone marrow study after two months of conservative management for Myelofibrosis is highly advocated in patients who have received Leflunomide which further offers a ray of hope for patients and avoids erroneously labelled diagnosis, unnecessary medications and agony.

Thus Reversible Myelofibrosis is an Enigma to Reckon, a Nightmare to Endure, and a Delight to Cherish.

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