

Case Report

JAK-2 positive Polycythemia Vera in a Rheumatoid Arthritis Patient: A Case Report and Literature Review

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ABSTRACT

Rheumatoid arthritis is a systemic inflammatory autoimmune disease of unknown etiology that initially present as a polyarthritis involving the small joints of the hands and the feet. As part of its systemic feature, the hematologic system can be affected in RA. The most common hematologic manifestation of RA is normochromic normocytic anemia of chronic disease or anemia from myelosuppression from disease modifying antirheumatic drugs. Polycythemia has been rarely reported in association with RA as most cases of polycythemia occurring in the setting of autoimmune diseases was seen with diseases other than RA. Given the association of RA with accelerated atherosclerosis and adverse cardiovascular outcome, the occurrence of polycythemia could increase the risk of a cardiovascular event. A rare case of JAK-2 positive polycythemia vera occurring in a 42-years old patient with established RA is presented in this report to heighten index of suspicion amongst clinicians and also to highlight management plan.

Keywords- Rheumatoid arthritis, Polycythemia vera, Janus Kinase-2.

INTRODUCTION

The coexistence of rheumatoid arthritis (RA) with polycythemia vera have been rarely reported in medical literatures. ^[1,2] Most cases of Myeloproliferative Neoplasia (MPN) coexisting with autoimmune disease mostly reported in association with diseases, other than RA, such as: psoriasis, Crohn's disease, systemic lupus erythematosus, localized scleroderma, autoimmune hemolytic anemia, polymyalgia rheumatica and reactive arthritis. ^[3] Patients with autoimmune disease have been noted to have a

20% increased risk of development of MPN, ^[3] with the highest risk being associated with reactive arthritis, giant cell arthritis or aplastic anemia. ^[3] The reason for development of MPN and other malignancies in patients with autoimmune diseases are not entirely known, though most studies have pointed to the prominent role that chronic inflammation plays in predisposing patients with autoimmune disease to cancers. ^[3,4,5] Chronic inflammation in autoimmune disease is hypothesized to serve as a constant stimulus of the immune system, which in turn results in rapid

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replication of immunoeffector cells with consequent production of aberrant cell clones that predispose to malignancy.^[5,6,7] Chronic inflammatory state promotes mutagenesis, defective tumor surveillance and immune dysregulation.^[5,6] It is also possible that both autoimmune disease and MPNs share a common etiopathogenic pathway.^[2] A pointer to the latter mechanism, is the commonality of shared predisposing genetic mutation in autoimmune diseases and cancers, eg Protein Tyrosine Phosphatase non receptor type 22 (PTPN) gene mutation and predisposition and MPNs.

Protein Tyrosine Phosphatase non receptor type 22 or Janus Kinase/ signal transducer and activator of transcription (JAK/STAT) gene are among the key regulatory proteins of the immune system that plays a vital role in controlling many physiologic processes. Genetic mutation in these regulatory proteins have been shown to predispose to a host of autoimmune diseases including rheumatoid arthritis and myeloproliferative neoplasia^[8-11]

CASE SUMMARY

A 41 years old house wife was first seen in July 2017 with complaints of recurrent polyarthritis affecting the small joints of the hands and feet associated with swelling and early morning stiffness of 1-year duration. She had early morning easy fatigue and occasional low to moderate grade fever. She had no oral mucosal ulcerations or skin rashes. There were no symptoms of uveitis, Raynaud's phenomenon or renal disease. She had glucose intolerance that is well controlled on therapeutic lifestyle measures.

General examination finding was unremarkable. Her chest was clinically clear, Blood pressure was 120/90mmHg. Musculoskeletal examination was significant for synovitis of the metacarpophalangeal joints of the right hand, right mid foot and bilateral metatarsophalangeal joints and the right knee.

Results of the patient's investigations were as follows- fasting blood sugar- 4.3mmol/L, 2 hours post prandial glucose was 6.7mmol/L, HbA1C

was-6.8%, urea, electrolytes, creatinine and liver enzymes tests were normal. Rheumatoid factor was positive, antinuclear antibody tests was negative. Serological test for Hepatitis B and C were negative and retroviral screening was negative for HIV 1 and 2 antibodies. The patients complete blood count and differential showed hematocrit-35.4%, total white blood cell count $-7.06 \times 10^9/L$, with a differential of lymphocyte-24.3%, neutrophils-69.3%, mid-6.4%, platelet count was 355×10^9 , erythrocyte sedimentation rate (ESR) was 40mm/Hr. Radiograph of the hand and feet showed soft tissue swelling and periarticular osteopenia, with no bone erosion noted.

A diagnosis of rheumatoid arthritis (RA) was made using the 2010 American college of Rheumatology (ACR) /European League Against Rheumatism (EULAR) classification criteria.^[12]

The patient was commenced on tabs Hydroxychloroquine sulfate 200mg twice daily, tabs

Methotrexate 20mg weekly, tabs folic acid 5mg weekly and prednisolone 5mg weekly. She was followed up at 2 monthly intervals and did complete blood count and differentials, in addition to kidney and renal function assessments a week prior to each clinic appointment. Her dose of methotrexate was increased 18th month into therapy to 25mg weekly on account of suboptimal RA disease control. At that point her ESR had risen to 50mm/Hr. Two years into follow up, Patient had complained of headache, blurred vision, tinnitus, vertigo and paresthesia of the hands and feet and her PCV was noted to be elevated-65.1%, Total WBC- $4.02 \times 10^9/L$, with differential of lymphocyte-34.2%, neutrophil-61.1%, mid-4.7% and a platelet count of $189 \times 10^9/L$. Chest radiograph and spirometry tests done to ascertain the cause of her polycythemia were both normal. Screening for Janus kinase-2 (JAK-2) mutation was positive. Based on the above, a diagnosis of polycythemia vera on a background of rheumatoid arthritis was made and tabs hydroxyurea 500mg daily and aspirin 75mg daily were added to her medications. She was to continue at her current

dose of methotrexate and hydroxychloroquine. The polycythemia responded to the addition of Hydroxyurea as evidence by resolution of hyperviscosity symptoms and reduction in the elevated PCV on 4th, 8th and 12th week of therapy was 40.6%, 36.3 and 35% respectively. The result of the full blood counts of the patients is depicted in table 1.

The patient is on follow up at both the rheumatology and hematology clinics and has remained in stable health.

Table 1: Serial results of Complete Count of RA patient at with Polycythemia rubra vera from diagnosis to follow up.

Timing	PCV (%)	TWBC(X 10 ⁹ L) ⁹	L(%)	N(%)	Mid(%)	Platelets(X 10 ⁹ /L)
At diagnosis	65.1	4.02	34.2	61.1	4.7	189
1-month later	40.6	6.48	38.2	59.6	0.14	401
2-month later	36.3	5.11	43.1	50.9	0.31	426
3-month later	35.0	5.4	35.5	58.9	0.3	381

DISCUSSION

The rheumatologic presentation of polycythemia vera includes joint aches and pains, bone pain (due to marrow expansion), or gouty arthritis; the latter occurring as a result of increased cell mass and turn over with resultant hyperuricemia. Gouty arthritis is even more widely reported to be associated with Polycythemia vera compared to RA^[13,14] Gouty arthritis typically presents in an ascending pattern, with arthritis afflicting the joints of the lower limbs in the initial stage of the disease before progressing proximally to involve joints of the upper extremities. Polycythemia induced gouty arthritis is associated with hyperuricemia, and the level of hyperuricemia closely reflects the frequency of attacks. The serum uric acid level of the patient remained normal throughout the period of follow up, thereby ruling out coexisting gouty arthritis. The index patient was treated for rheumatoid arthritis with methotrexate for 2 years prior to the onset of polycythemia. Hydroxyurea was added following the diagnosis of polycythemia vera to good clinical and hematologic effect as evidenced by resolution of the hyper viscosity symptoms and reduction in the patient's high red cell mass with

consequent progressive reduction in values of packed cell volume until a normal PCV level was attained and sustained thereafter. Methotrexate was continued in the patient as it has a dual benefit of being an anchor drug in the management of RA as well as its beneficial effect in patients with MPN.^[15,16]

Recent studies have alluded to the benefit of methotrexate in the management of MPN.^[15,16] Methotrexate has been hypothesized to exert its effect on PMN via suppression of the janus kinase/ (JAK/STAT) pathway,^[17] which is a key pathway in the etiopathogenesis of polycythemia vera.^[10] Our patient was on methotrexate for 2 years before the onset of polycythemia rubra vera. Her development of PMN while on methotrexate could be a pointer to the fact that though methotrexate might be beneficial in the treatment of polycythemia, it might have no prophylactic effect on the development of PMN in patients with rheumatoid arthritis. The impact of prior exposure to methotrexate on the clinical expression /severity of polycythemia in this patient cannot also be safely inferred.

Given the patient response to hydroxyurea, we had no recourse to Janus Kinase inhibitor (Jak inhibitors) in the patient's management. Janus Kinase has been shown to be effective in the individual management of both Rheumatoid arthritis^[18,19] and MPN^[19,20] and might be considered as 1st line therapy in patients with rheumatoid arthritis coexisting with MPN.

The occurrence of polycythemia vera in an RA patient presents a heightened risk of adverse outcome in the patient, particularly with regards to cardiovascular disease. Both RA and PMN are known to be independently predispose to adverse cardiovascular outcome. Rheumatoid arthritis induced cardiovascular diseases are mainly mediated via accelerated atherosclerosis.^[21] Whereas patients with standalone MPN have been shown to have higher mortality rates mostly due to adverse cardiovascular events, increased infections rate and leukemic transformation.^[22] It is possible that a summation of the cardiovascular

risks of MPN and RA could impact negatively on the patient, if not well attended to. Hence the need to regularly screen RA patients on follow up by doing periodic complete blood count and to be on the lookout for the occasional patients that will present with polycythemia.

CONCLUSION

Myeloproliferative neoplasia (polycythemia vera) can complicate RA. Prompt diagnosis and treatment with Hydroxyurea and continuation of methotrexate was beneficial with regards to cytoreduction and symptomatic improvement in our patient.

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