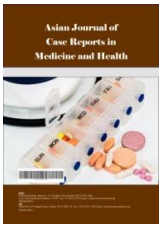

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Successful Treatment of Clonal Eosinophilia with FIP1L1-PDGFRA Rearrangement with Low Dose IMATINIB – A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Author KHBPF Patient diagnosis and follow up, conception of manuscript, writing up the manuscript, editing and formatting manuscript to journal specifications, author CCG patient follow up ,recording clinical details, writing manuscript . Author BJ patient diagnosis and follow up. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Clonal eosinophilia with FIP1L1-PDGFRA rearrangement is a rare disorder which is almost exclusively seen in males. Targeted therapy with Imatinib has led to successful achievement of molecular remission of this disorder but no evidence exists for continuous or maintenance therapy or treatment free remission yet. This is a case of clonal eosinophilia with FIP1L1-PDGFRA rearrangement in a young man, who presented with very high eosinophil and neutrophil counts, moderate thrombocytopenia, hepatosplenomegaly and skin and lung involvement. Imatinib at 100mg daily was started after initial treatment with cytoreductive therapy and steroids. He responded well to low dose Imatinib with complete absence of symptoms and normalization of counts within 3 months and disappearance of molecular evidence of the disease following 2 years of therapy. Imatinib was then tailed off and he remains asymptomatic on a weekly dose of 100mg Imatinib. Workup towards a diagnosis of eosinophilia has been made easy with the new classification and inclusion of molecular evaluation. The high eosinophil count, presence of organomegaly and thrombocytopenia favoured a clonal aetiology .Low dose Imatinib gives

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excellent clinical, haematological and molecular remission and can be safely reduced thereafter to weekly maintenance.

Keywords: Clonal eosinophilia, Imatinib, FIP1L1-PDGFRA rearrangement.

ABBREVIATIONS

MLN E0 :*Myeloid Lymphoid Neoplasms with eosinophilia*
FIP1L1/PDGFRA :*FIP1-like-1-platelet-derived growth factor receptor-alpha*
FIP1L1/PDGFRB :*FIP1-like-1-platelet-derived growth factor receptor-Beta*
FISH :*Fluorescence in situ hybridization*

1. BACKGROUND

Eosinophilia is defined as an elevation of the eosinophil count above normal, i.e. above 0.5 x 10^9/L. Causes for eosinophilia are categorized as primary (Clonal eosinophilia MLN-E0), secondary (reactive) which is the commonest type and idiopathic [1,2] Primary or Clonal eosinophilia refers to a disease entity where the eosinophilia occurs as a part of the neoplastic clone in a haematological neoplasm and is further subcategorized as myeloid variant, clonal eosinophila with recurrent molecular abnormalities and chronic eosinophilic leukaemia not otherwise specified (CEL NOS). [3,4] Clonal eosinophilia with recurrent molecular abnormalities is relatively uncommon and includes acquired genetic abnormalities that include the genes PDGFRA,PDGFRB,FGFR1 and JAK2 .The most common among them is the FIP1L1-PDGFRA rearrangement [3,4] Clonal eosinophilia should also be considered in patients presenting with unexplained isolated eosinophilia of > 1.5 x l 0^9/L in the absence of a reactive aetiology , because it can be treated according to the respective molecular target, the tyrosine kinase inhibitor , Imatinib mesylate with the achievement of molecular remission [5] Although evidence shows that discontinuation is associated with relapse there is no evidence on duration of long term low dose maintenance therapy.

2. CASE PRESENTATION

A 39 year old man, who was previously well, presented with a 2 months history of significant constitutional symptoms including evening pyrexia, loss of weight, loss of appetite, left hypochondrial pain and pruritus. He also had productive cough for 3 weeks. He had been working in Saudi Arabia as a heavy-vehicle driver for the last 2 years.

On physical examination he was afebrile and had a few coarse crepitations in his bilateral lung fields, a palpable firm spleen 4 cm below the left costal margin and a palpable liver of 2 cm. There was no lymphadenopathy, skin rashes or lesions or peripheral stigmata of connective tissue disorder. The rest of the systemic examination was unremarkable.

He had a marked leucocytosis (Total WBC count of 76.21 x 10^9/L) with marked neutrophilia and eosinophilia(Absolute neutrophil count - 43.89 x 10^9/L ; Absolute eosinophil count - 27.02 x 10^9/L) and moderate thrombocytopenia (67 x 10^9/L) .

Investigations done to exclude reactive causes of eosinophilia, including tests for parasitic infections, allergy and autoimmune causes were negative.

USS abdomen revealed splenomegaly of 17cm and hepatomegaly of 16.3cm. Chest X ray showed mild inflammatory shadows bilaterally and CRP was raised (245 mg/L) but both resolved as treatment for a concurrent lower respiratory tract infection was initiated.

Investigations to exclude end organ damage due to eosinophilia did not show any abnormality.Bone marrow aspiration and trephine were markedly hypercelluar with granulocytic hyperplasia and left shifted maturation with 2% blasts ; Markedly increased eosinophils and eosinophil precursors was seen with normal erythropoiesis and megakaryopoiesis. No significant dysplasia was present and the reticulin stain was grade 0.There was no evidence of lymphoma, leukaemia or granuloma formation seen.

As the absence of a reactive cause, presence of hepatosplenomegaly, moderate thrombocytopenia and very high eosinophil counts suggested a clonal aetiology, genetic studies were done which confirmed the presence of FIP1L1-PDGFRA rearrangement by FISH.

Table 1. Relevant Investigations

Test	Result
Full blood count	Total WBC 76.21 x 10^9/L Neutrophils 43.89 x 10^9/L Lymphocytes 2.87 x 10^9/L Eosinophils 27.02 x 10^9/L Haemoglobin 12.1 g/dL Platelets 67 x 10^9/L
Blood picture	Normochromic normocytic red cells with moderate rouleaux formation Marked leucocytosis with neutrophilia and a left shift with few myelocytes Severe eosinophilia, most with normal morphology and a few degranulating forms. No circulating blasts. Moderate thrombocytopenia
Bone marrow biopsy	Markedly hypercelluar with granulocytic hyperplasia and left shifted maturation with 2% blasts.Markedly increased eosinophils and eosinophil precursors seen with normal erythropoiesis and megakaryopoiesis. No significant dysplasia and the reticulin stain was grade 0. No evidence of lymphoma,leukaemia or granuloma formation seen.
Erythrocyte sedimentation rate	42 mm 1st hour
C reactive protein	245 mg/L, later came following resolution of the lower respiratory tract infection he had.
Liver functions Renal functions Uric acid level	Normal
Chest X ray	Mild inflammatory shadows bilaterally
Electrocardiogram Echocardiogram	Normal
Troponin I	Negative
Ultrasound abdomen and pelvis	Splenomegaly 17cm, Hepatomegaly 16.3cm, no abdominal lymphadenopathy or other masses
Serum Ig E level	Normal
Skin prick test for specific allergen	Negative
Serology – filariasis, toxocariasis Stool - microscopy for ova, cysts, parasites Urine for schistosoma	Negative
Antinuclear antibody test, ds DNA, Rheumatoid factor	Negative
FIP1L1-PDGFRA rearrangement by FISH	Detected
BCR-ABL1 rearrangement by PCR	Not detected

With the detection of FIP1L1-PDGFRA rearrangement a diagnosis of Clonal eosinophilia with FIP1L1-PDGFRA rearrangement was made and he was started on Imatinib a tyrosine kinase inhibitor at a daily dose of 100mg and showed a satisfactory haematological response with normalization of blood counts, resolution of symptoms and splenomegaly within 3 months.

Imatinib was continued at a dose of 100mg daily for 2 years and patient was free of symptoms and maintained the same haematological response throughout. After completion of 2 years of treatment repeat FIP1L1-PDGFRA rearrangement was negative suggestive of molecular remission. We are still continuing Imatinib at a low dose but at a reducing frequency of weekly dosing to which he continues to show normal clinical and laboratory findings.

3. DISCUSSION

Work up for diagnosis of eosinophilia involves initial exclusion of reactive /secondary causes. In the tropical and subtropical countries parasitic infections form a main entity .As the patient had returned from the Middle East this further increased the probable diseases as infections that are not commonly seen in Sri Lanka such as schistosomiasis needed exclusion. At the same time other causes such as allergies and vasculitis (which are more common in the West) were also investigated for. Although high eosinophil count was more suggestive of a clonal eosinophilia rather than reactive, very high counts have been reported with reactive causes. Thus emphasis on travel history, drug history , physical examination, investigations to exclude parasitic infestations , allergies and autoimmune disorders formed a main part of our initial workup. The presence of hepatosplenomegaly and moderate thrombocytopenia were more robust clues towards a clonal aetiology. FIP1L1-PDGFRA is the most common gene rearrangement accounting for 14 % of all primary eosinphilias. [6] Therefore in a resource restricted setting like Sri Lanka where the government spends for patients undergoing treatment at state hospitals a decision was made to investigate only for this gene rearrangement. Clonal eosinophilia with FIP1L1- PDGFRA rearrangement is an uncommon disorder, which is known to respond well to the tyrosine kinase inhibitor, Imatinib Mesylate at a low close. [5] However at presentation the patient had a very high eosinophil count which in part was contributing to his respiratory symptoms together with the concurrent infection. Therefore prior to initiating treatment with Imatinib and while awaiting the genetic results we initiated cytoreduction with Hydroxyuria 1g BD initially with 20 mg of prednisolone under antibiotic cover for the infection. With response this was later tailed off and omitted and Imatinib was started at 100mg/d. Although imatinib is the treatment of choice for FIP1L1/PDGFRA-positive clonal eosinophilia and many studies show that low dose Imatinib has a good response very little data is available on duration of treatment and the risk of relapse following discontinuation. Small study series have shown good responses with molecular remission with 100mg/d dosing. [5,7] Available data suggest continuation of treatment at reduced frequency of dosing with molecular monitoring with no definite recommendations for treatment discontinuation. In one study involving 5 patients with FIP1L1/PDGFRA-positive CEL with documented clinical, hematologic, and molecular remission on imatinib 400 mg daily a dose de-escalation trial was tried. Molecular relapse occurred in one patient after 5 months on dose de escalation when on a daily dose of 100 mg. The remaining relapsed after discontinuation of Imatinib at a median time of 25.5 months (range, 19-31 months). [8] In another study 11 patients achieved molecular remission. However in two patients ,withdrawal of imatinib was followed by a rapid rise in FIP1L1-PDGFRA transcript levels [9] Data from another study suggests that a single weekly dose of imatinib is sufficient to maintain remission in FIP1L1-PDGFRA- positive CEL patients. [10,11] In a phase-II study evaluating the long term adverse effects of Imatinib it was concluded that overall, imatinib was well tolerated with a low incidence of grade III/IV toxicities [12] In our patient we continued 100mg/d for 2 years , achieved FIP1L1-PDGFRA negativity and have reduced the dosing through alternate day de-escalation to weekly dosing to which he shows good response with no side effects of treatment. This corresponds to data from other case reports and studies that have shown good response with weekly maintenance with very little adverse effects with long term Imatinib. However discontinuation of Imatinib will need to be based on further data as so far data has shown increased relapse rates with discontinuation.

4. CONCLUSION

Workup towards a diagnosis of eosinophilia has been made easy with the new classification and directions available in current literature where after exclusion of recognized secondary causes molecular evaluation needs to be done. The eosinophil count , presence of organomegaly and thrombocytopenia favoured a clonal aetiology . Patients with high counts and symptoms related to eosinophilia benefit from cytoreductive therapy

and steroids while awaiting initiation of Tyrosine Kinase inhibitors.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

AVAILABILITY OF DATA AND MATERIALS

Patient management details are available in his hospital records and clinic notes and copies can be made available.

CONSENT

The patient has provided informed consent for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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