Myeloproliferative Neoplasm with Prominent Eosinophilia

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Summary:
The patient, a young soldier aged 36 years having past history of malaria, was admitted in CMH Dhaka on 17 August 2011 as a transferred case from CMH Saidpur and died on 22 August 2011. The deceased was admitted in CMH Saidpur on 05 August 2011 with high fever for 05 days along with generalized joint and muscle pain. In spite of all available treatment the patient was deteriorating and he was then transferred to CMH Dhaka. At that time the patient was febrile, dehydrated and toxic with lymphadenopathy, extremely tender joints and muscles. The patient rapidly developed acute kidney failure and gradually developed features of DIC. His bone marrow examination revealed dyserythropoiesis with predominantly eosinophilic granulopoiesis, suggestive of myeloproliferative neoplasm with prominent eosinophilia. The patient was treated with injectable antibiotics, antimalarial and oral prednisolone with all intensive care facilities. Ultimately all attempts were proved unsuccessful and he died on 22 August 2011 at 1700 hrs. On autopsy the deceased had intra atrial thrombus and possibly that was the immediate cause of death. A haematological malignancy, myeloproliferative neoplasm with prominent eosinophilia, can very well produce such a fatal condition.

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Case Report:
The deceased, a young soldier of 36 years, was admitted to CMH Saidpur on 05 August 2011 with high fever for 05 days along with generalized joint and muscle pain. His urine R/E revealed 18-20 pus cells/HPF and widal test was positive (TO1:160). He was treated with sufficient dosage of inj Ceftriaxone and Doxycycline. Because of severe pain he was also given Diclofenac orally. During this time his serum albumin was found to be 17 gm/L and there was bilateral small renal calculi without any feature of obstruction. His urine culture was negative. His fever and pain continued, Ofloxacin and Quinine was added in the place of ceftriaxone (patient served in CHT and had malaria in the past). Inspite of all the above, the patient was deteriorating and he was then transferred to CMH Dhaka. The patient was febrile, dehydrated and toxic with extremely tender joints and muscles. There were palpable lymphnodes at the inguinal and cervical areas and mild hepatomegaly. Sufficient rehydration was done, Ofloxacin continued and oral prednisolone was advised considering a patient of polymyositis. His PBF report revealed Leuco-erythroblastic blood picture with thrombocytopenia (Total count was 30x10⁹/L, N-78%, E-14% Myelocyte 2% with

Introduction:
Eosinophilia is commonly observed in a wide range of non-clonal and clonal disorders. In the majority of cases it is reactive associated with atopic conditions, autoimmune disorders, infections or malignancies. In rare cases, a haematologic disorder underlies sustained eosinophilia which can be either non-clonal or clonal. Idiopathic hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia (CEL) comprise a spectrum of indolent to aggressive disease characterized by unexplained, persistent hypereosinophilia. Myeloproliferative and lymphoid neoplasms associated with rearrangement of platelet-derived growth factor receptor α (PDGFRα), platelet-derived growth factor receptor β (PDGFRβ), fibroblast growth factor receptor 1 (FGFR1) are three rare specific disease groups, which have some shared features and some that differ. Clonal or primary eosinophilia is generally associated with chronic myeloproliferative disorders (Eos-MPD). Chronic eosinophilic leukemia (CEL) is diagnosed in the presence of increased numbers of blasts and/or clonality through cytogenetic or molecular analyses.¹ ²

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few promyelocyte and platelet count was 91x10⁹/L). Along with steroid his antibiotics was adjusted with Inj Meropenem and Inj. Clarithromycin. Inspite of every thing, the patient rapidly developed acute kidney injury with serum creatinine of 6.5 mg/dl and metabolic acidosis with Ph of 7.2. Patient become unconscious and also developed generalized seizure. He was given assisted ventilation and peritoneal dialysis was done. He was also given Inj Albumin and combination of anti malarial (Artemether+ Lumefantrine). Gradually he developed features of DIC (Bilirubin 2-5 mg/dl, ALT-30 U/L, Alk phosphatase -82 U/L, LDH-3649 mg/dl, PT-20 (control-12), APTT-45 (control 30), FDP>5 µmol/L and thrombocytopenia). His bone marrow examination revealed dyserythro-poiesis with predominantly eosinophilic granulopoiesis, suggestive of myeloproliferative neoplasm with prominent eosinophilia. Ultimately all attempts were proved unsuccessful and he died on 22 August 2011 at 1700 hrs.

Postmortem examination revealed a mural thrombus in the right atrium. Considering all the above facts, the deceased had following important features. a. High fever, polyarthritis and tender painful muscles. b. Lymphadenopathy. c. Pyrexia. d. Hypoalbuminaemia, raised TO in widal test, subsequently he also had: e. Rapid development of AKI and acidosis. f. Leuco-erythroblastic blood picture with thrombocytopenia, eosinophilia and bone marrow evidence of MPN with prominent eosinophilia. Chronic eosinophilic leukaemia and HES is excluded by the presence of <5% blasts in bone marrow and eosinophilia associated with features of myeloproliferative syndrome³ (including organomegaly neutrophilia, circulating myelocytes and erythroblasts, hyperplastic bone marrow) respectively. g. Features of DIC. h. Right atrial thrombus.

Fig.-1: Peripheral blood film.

Fig.-2: Bone marrow (Low power view)

Fig.-3: Bone marrow (High power view)

Fig.-4: Intact coronary artery (Microscopic view)
At CMH Saidpur, after admission and subsequently also, the deceased had persistent hypoalbuminaemia. There is no obvious cause about this very important marker of chronic illness, in that there is no history of malnutrition, jaundice or renal problem in the past. It could be due to presence of an indolent haematological malignancy which was sub-clinical or due to a connective tissue disease (Polymyositis). After admission there was pyuria, though sufficient antibiotic was given, in an immunocompromised state, UTI can cause sepsicaemia and ultimately DIC. The deceased had intra atrial thrombus and possibly that was the immediate cause of death. Presence of thrombus indicates a pro-coagulant state. A haematological malignancy can very well produce such a condition. So finally considering all the evidences above, the mode of death was due to cardiac arrest form intra-atrial thrombus. The primary cause of which was a haematological malignancy i.e Myeloproliferative neoplasm with prominent eosinophilia.

Discussion:
The 2008 World Health Organization (WHO) classification of tumors of haematopoietic and lymphoid tissues introduced a new category for myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRα, PDGFRβ or FGFR1. Many of these cases present as a myeloproliferative neoplasm, usually with eosinophilia. However, neoplasms associated with rearrangement of PDGFRα can present as acute myeloid leukemia or T lymphoblastic lymphoma, in both instances with eosinophilia, and both T lymphoblastic and B lymphoblastic transformation of chronic eosinophilic leukemia have also been described. Because of the prominent lymphoid component these disorders have been assigned, in the WHO classification, to a specific category rather than being categorized as a myeloproliferative neoplasm (MPN). However, it should be noted that BCR- ABL1-positive chronic myelogenous leukemia is accepted as a bonafide myeloproliferative neoplasm and yet it too can undergo lymphoblastic transformation and even present as acute lymphoblastic leukemia with the underlying chronic myelogenous leukemia being revealed only after remission has been achieved. In the case of PDGFRβ-related disease, the features of MPN are more variable but are often those of chronic myelomonocytic leukemia (CMML) with eosinophilia.

Chusid et al in 1975 used 3 diagnostic criteria for HES that are still utilized today: (1) persistent eosinophilia of 1.5x10^9/L (1500/mm^3) for longer than 6 months; (2) lack of evidence for parasitic, allergic, or other known causes of eosinophilia;and (3) signs and symptoms of organ involvement. In the recent World Health Organization (WHO) classification, a diagnosis of HES or CEL requires exclusion of reactive causes of eosinophilia and malignancies. In this scheme, blood eosinophilia is divided into 3 categories: reactive (nonclonal eosinophilia), clonal disorders of the bone marrow associated with eosinophilia, and HES, which remains a diagnosis of exclusion.

Acquired constitutive activation of protein tyrosine kinases is a central feature in the pathogenesis of chronic MPD. Activation occurs as a consequence of specific point mutations, e.g. JAK2 V617F, or fusion genes, e.g. BCR-ABL, generated by chromosomal translocations, insertions or deletions. In Eos-MPD, cytogenetic analysis has identified four distinct recurrent breakpoint clusters that target the genes encoding PDGFRα at 4q12, PDGFRβ at 5q31-33, FGFR1 at 8p11 and janus kinase 2 (JAK2) at 9p24. To date, more than 35 different fusion genes have been identified in association with Eos-MPD, the most common of which is FIP1L1-PDGFRα, generated by a cytogenetically invisible 800kb interstitial deletion on chromosome 4q12.
Clonal or primary eosinophilia is generally associated with chronic myeloproliferative disorders (Eos-MPD) which is a potentially life-threatening condition associated with end-organ damage to heart, gastrointestinal tract, skin, joints or nervous system due to release of granular contents from infiltrating eosinophils. The most common presenting signs and symptoms were weakness and fatigue (26%), cough (24%), dyspnea (16%), myalgias or angioedema (14%), rash or fever (12%), and rhinitis (10%). In many cases lymphadenopathy is present at diagnosis whereas in others it appears during the course of the disease. The most striking clinical feature, similar to PDGFR-related disorders, is a marked male predominance. The majority of patients have organ and systemic involvement like blood, heart, spleen, liver, lung, nervous system and especially, skin involvement.

The most serious clinical findings relate to endomyocardial fibrosis, with ensuing restrictive cardiomegaly. Scarring of the mitral/tricuspid valves leads to valvular regurgitation and formation of intracardiac thrombi, which may embolize to the brain or elsewhere. Peripheral neuropathy, central nervous system dysfunction, pulmonary symptoms due to lung infiltration, and rheumatological findings are other frequent manifestations.

The effectiveness of imatinib for myeloproliferative HES has revolutionized treatment of this disease. Many patients can be managed utilizing relatively low doses of imatinib, 100–200 mg/week, with complete clinical and molecular control. Before commencing treatment with imatinib, troponin should be measured because of the danger of eosinophilic myocarditis and treatment with glucocorticoids may be required. Cases of primary resistance to imatinib has also been identified. Treatment of patients with myeloproliferative HES lacking FIP1L1-PDGFRα can present a considerable challenge, and one must resort to the medications including prednisolone, hydroxyurea and interferon-α. A monoclonal antibody to IL-5, mepolizumab, is also used.
Conclusion:
Myeloproliferative and lymphoid neoplasms associated with rearrangement of PDGFRα, PDGFRβ and FGFR1 constitute three rare specific disease groups, in whom eosinophilia is characteristic. The identification of FIP1L1-PDGFRα in cases of HES adds to a growing list of activated fusion tyrosine kinases linked to the pathogenesis of chronic myeloproliferative disorders. It is unique but the relative rarity of this molecular genetic analysis would represent a considerable challenge. However, circumstantial evidences could be gained to address this condition. The overall prognosis is currently poor. In fact, this discussion points to the rapid pace of progress in the understanding of diagnosis and management including several kinase inhibitors, are on the horizon, to treat myeloproliferative neoplasm with prominent eosinophilia.

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