Philadelphia Chromosome Positive Essential Thrombocythemia with Dilated Cardiomyopathy

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Abstract
We report here an unusual case of a 30-year old male patient with essential thrombocythemia (ET) and dilated cardiomyopathy, who on further investigation was found to have Philadelphia chromosome positive (Ph+) cells in the bone marrow. The reverse transcriptase-polymerase chain reaction (RT-PCR) test on his peripheral blood leucocytes revealed b2a2 transcript of the bcr-abl fusion gene. Literature shows that the boundary line between Ph+ essential thrombocythemia and chronic myeloid leukemia (CML) is getting blurred day by day. Each one may be a part of the spectrum of a single clonal proliferative disease. Association of dilated cardiomyopathy with ET has not been reported. ©

INTRODUCTION
Essential thrombocythemia (other designations include essential thrombocytosis, idiopathic thrombocythosis, primary thrombocytosis, hemorrhagic thrombocythemia) is a clonal disorder of unknown etiology involving a multipotent hematopoietic progenitor cell and is manifested clinically by the overproduction of platelets without a definable cause.1,2 No clonal marker distinguishes it from the commoner nonclonal reactive causes of thrombocytosis. In a recent report, 13.3% cases of ET were found to be Ph+.3 Ph+ cases had smaller megakaryocytes with hypolobulated nuclei and were more prone to transform into CML, blast crisis and myelofibrosis.4 It was suggested that both Ph+ ET and the thrombocytosis associated with CML could be regarded as early manifestations of the chronic stable phase of CML. However, other investigators reported that transformation to chronic myeloid leukemia type of disease or acceleration/blastic crisis was not observed in the bcr+ ET patients. Neither did these patients differ significantly from typical ET patients in quantitative indices of bone marrow cellularity or the size of megakaryocytes.5 Thus the exact clinical, cytogenetic and morphometric relationship between Ph+ ET and CML is as yet undetermined. Patients with ET are more prone to suffer from thrombohemorrhagic complications.6 Presence of global systolic dysfunction without any regional wall motion abnormality suggests that abnormal thrombosis of the major coronary arteries was not the cause of dilated cardiomyopathy in our patient.

CASE REPORT
30-year old Hindu male living in Palashi, Nadia, West Bengal, hair dresser by occupation, presented with the chief complaints of progressive weight loss for 5 months and exertional breathlessness for 2 months. There was a cumulative loss of >30% of the body weight over the last 5 months without any symptoms suggestive of diabetes mellitus, thyrotoxicosis, gastrointestinal disease, poor intake or lump anywhere. Exertional breathlessness was NYHA Class III in severity, without any fever, cough, sputum production, hemoptysis, chest pain or seasonal variation. There was a history suggestive of paroxysmal nocturnal dyspnea several times over the last one month but history of palpitation, precordial chest pain, syncope or pre-syncope, leg or abdominal swelling and urinary symptoms were absent. Patient had no history of bone or joint pain, skin rash or pigmentation, purpuric spots or bleeding manifestations, motor or sensory symptoms, headache, altered consciousness or convulsions. There was no significant past or family history. The patient was married and was having two healthy children. There was no history of sexual exposure or high-risk behavior.

On examination
Wasted facies with evidences of undernutrition; Weight-48 kg; BMI-17.6; moderate pallor; Multiple, 1-1.5 cm, discrete, firm, non-tender lymph nodes in left cervical, right axillary and both inguinal regions; Pulse-108/min, regular; BP- 110/68 (supine); Respiration-22/min; Temperature- normal; Spleen- 2 cm below left costal arch, firm, smooth, non-tender; Liver- not enlarged; Cardiac apex- at left 6th ICS, 1.25 cm outside MCL, LV type; LV S3 present; Bilateral end-inspiratory fine
crepitations over lung bases. Other findings were within normal limits.

**Laboratory investigation**

Routine blood:- Hb-7.7gm/dl; Erythrocyte-3,340,000/mm³; PCV-25.4%; MCV-74.5fl; MCH-22.6 pg; MCHC-30.3 g/dl; Reticulocyte-1%; TLC-12,500/mm³; PMN-83%; Lymphocyte-6%; Monocyte-2%; Eosinophil-1%; Basophil-8%; Platelets-22,45,000/mm³; ESR-32mm in 1st hr. Routine urine and stool: - Normal. ECG:- Sinus tachycardia; non-specific ST-T changes in the precordial leads. CXR:- Features of pulmonary edema with increased cardio-thoracic ratio; prominence of horizontal fissure; tenting of right dome of diaphragm. Sputum for AFBx3:-Negative. HIV I and II serology:-negative. Echocardiography:- Enlarged ventricles and atria; global systolic dysfunction; ejection fraction-38%; trivial mitral regurgitation. Impression- Dilated cardiomyopathy. Upper GI Endoscopy:- Esophagitis due to candidiasis. Bleeding time, prothrombin time and activated partial thromboplastin time:-Normal. Bone Marrow Examination:- Cellular marrow; megakaryocytes increased in number with both active and inactive forms present; erythropoiesis normoblastic with mild hyperplasia; occasional megaloblastoid cells present; leucopoiesis unremarkable; lymphoid series within normal limits; plasma cells occasional; no marrow infiltration or metastatic deposits seen; no parasites found; Pearl stain- stainable iron present. Impression- marrow picture is suggestive of essential thrombocythemia. Lymph node biopsy:- Necrotizing lymphadenitis; may be due to ischemic necrosis due to abnormal thrombosis; Reticulin stain- normal nodal architecture seen; PAS stain- no remarkable abnormality except necrosis. Karyotyping and G-banding:-
Philadelphia chromosome present in about 30% of cells in the bone marrow. Reverse transcriptase-polymerase chain reaction (RT-PCR): B2a2 transcript of bcr-abl fusion gene (210 kilo dalton protein) is present in the peripheral blood leucocytes, i.e., exon 13 of bcr gene (chromosome 22) is fused with exon 2 of abl gene (chromosome 9).

**Discussion**

Ph+ ET is a rare entity. Mitchiels *et al* reported that the presence in the bone marrow of an increased number of active megakaryocytes which are smaller than normal and possessing hypolobulated nuclei in patients with pronounced thrombocytosis and no evidence of CML gave the diagnosis. In contrast, Ph-negative ET patients had mature and enlarged megakaryocytes arranged in clusters in the bone marrow. They suggested that both Ph+ ET and thrombocytosis associated with CML could be regarded as early manifestations of the chronic stable phase of CML. However, in a study on 63 patients with myeloproliferative disorders [including CML, ET, and polycythemia vera (PV)] and 51 normal, healthy volunteers, bcr-abl transcript was detected in 4 of 30 ET patients (13.3%), 17 of 17 CML patients (100%), none of 16 PV patients (0%), and 1 of 51 normal subjects (1.9%); further semi quantitative analysis showed that the intensity of bcr-abl transcript expression in the 4 ET patients and the single normal individual was 10³ to 10⁶ times less than that in the CML patients. In another study on 64 consecutive patients meeting the criteria of ET, bcr-abl expression was found in 6 patients by RT-PCR and Ph+ mitoses in the bone marrow in 3 of them by conventional cytogenetic analysis. During an average of 57-month long follow-up, no transformation to CML type of myeloproliferation could be observed in the Ph+ ET patients. These patients did not differ significantly from typical ET patients in quantitative indices of bone marrow cellularity or the size of megakaryocytes. In these two parameters as well as in the total nucleolus organizer region area per nucleus, however, significant differences could be detected between these patients as well as typical CML patients. Statistical analysis of the morphometric data obtained from all the Ph+ and bcr+ ET patients combined indicated a shift of the bone marrow morphology towards the CML type of myeloproliferation. They suggested that bcr+ ET resembles ET more closely than CML and bcr+ ET was not a forme fruste of CML; various expansions of the Ph+ clone appear to lead to either ET or CML type of myeloproliferation. It remains to be seen whether both these diseases should be considered as part of the spectrum of a single clonal disorder. The presence of dilated cardiomyopathy in our case is an unusual finding and its relation with ET remains unresolved. Thrombohemorrhagic complications occur in myeloproliferative disorders including ET and more so in the group with platelet counts of <10,000,000/mm³. Absence of regional wall motion abnormality in the echocardiography with dilatation of all four chambers of the heart and global systolic dysfunction does not favor ischemia due to abnormal thrombosis of the major coronary arteries as the cause of cardiomegaly and heart failure in our patient. Association of dilated cardiomyopathy with ET has not been reported in the literature.

**References**


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**Announcement**

**NAPCON – 2005**

7th Joint Annual Conference of Indian Chest Society and National College of Chest Physicians of India. 16-20 November, 2005 at Science City, Kolkata.

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