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Case report 2

Chronic myeloid leukaemia with generalized lymphadenopathy – a high risk category

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Abstract

Chronic myeloid leukaemia (CML) presenting with generalized lymphadenopathy is an uncommon manifestation of CML. Lymphadenopathy in these patients could be due to extramedullary involvement by myeloid cells with all stages of maturation, blast infiltration, co-existing lymphoproliferative disorder or reactive lymphadenopathy. We report a case of a 38-year-old male with CML in chronic phase and generalized lymphadenopathy at diagnosis. He transformed to blast crisis within 14 weeks of diagnosis despite tyrosine kinase inhibitor (TKI) therapy. This case indicates that CML patients with lymphadenopathy are at high risk of disease progression and early blast transformation and therefore candidates for aggressive treatment.

Case report

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm with a distinct genetic abnormality: BCR-ABL1 fusion gene resulting from the Philadelphia chromosome[1]. CML is commonly diagnosed with incidental leucocytosis or due to constitutional symptoms[2]. There are many atypical presentations of CML. Prognostic significance of these uncommon presentations are still not extensively studied. CML patients presenting with lymphadenopathy is an uncommon manifestation which has a prognostic significance. There are few reported cases of lymphoma coexisting with CML[3,4,5,6]. Both Hodgkin and non-Hodgkin lymphomas have been reported in these patients. Here we describe a case of CML with generalized lymphadenopathy at initial presentation in a young male, who progressed in to blast crisis within a short period of time after diagnosis. A 38-year-old male with type 2 diabetes mellitus with a good glycaemic control, presented to haematology department with low grade fever, night sweats, and weight loss of >10% over 3 months. Associated early satiety and exertional dyspnoea for 2 months and worsening of symptoms over the last 2 weeks. ECOG performance state was-2. Physical examination revealed generalized non-tender lymphadenopathy involving right cervical, axillary and inguinal regions. Abdominal examination revealed a massive firm non-tender splenomegaly measuring 32 cm and mild hepatomegaly. Other system examination was unremarkable. His full blood count showed marked leucocytosis with WBC-316.45×10^9/L, Hb7.5 g/dL, PLT 45×10^9/L. Peripheral smear showed typical CML morphology with marked leucocytosis with full spectrum of granulocytic maturation with peaks of mature neutrophils and myelocytes. Eosinophilia and basophilia were seen with occasional blasts (<1%). Differential count showed segmented neutrophils 40%, metamyelocytes 16%, myelocytes 26%, promyelocytes 12%, lymphocytes 2%, eosinophils 3%, basophils 1% (Figure 1). Bone marrow was markedly hypercellular with marked granulocytic hyperplasia. Megakaryopoiesis was moderately hypercellular with dwarf megakaryocytes and few in loose clusters. Mildly increased interstitially scattered lymphoid cells were seen with few small lymphoid collections. No morphological evidence of excess of blasts was noted. Immunohistochemistry (IHC) of CD3 and CD20 showed a reactive pattern of distribution. Reticulin stain showed reticulin fibrosis of WHO-MF 1-2. RT-PCR from peripheral blood for BCR ABL1 showed p210

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transcripts. Cytogenetic studies were not done due to financial constraints. Serum LDH was raised to 1482 U/L with mild increase in liver transaminases. Rest of the serum biochemistry were within the normal limits. ESR was 24mm/hour. Since the patient had generalized lymphadenopathy further investigations were done to rule out a co-existing lymphoma and extramedullary blast proliferation. CECT of chest, neck and abdomen confirmed hepatosplenomegaly with a 39 cm spleen extending up to the right iliac fossa. Prominent peripheral lymph nodes and aorto-caval nodes were noted. Histology of a left inguinal lymph node showed partially effaced architecture with diffuse areas showing poly-morphic population of cells comprising lymphocytes, eosinophils, neutrophils with scattered atypical cells. IHC of these atypical cells were negative for CD3, CD20, CD15, CD30, CD23, CD34 but showed strong cytoplasmic positivity for MPO (Figure 2). Lymph node biopsy findings were consistent with CML. There was no evidence of clonal expansion of B or T lymphocytes or NK cell population in bone marrow by flow cytometry. Based on above findings the diagnosis of CML in chronic phase was made. His ELTS score was 4.1 (High risk score). He was started on imatinib 400mg/day. With treatment, splenomegaly and lymphadenopathy gradually improved and FBC parameters became normal within 1 month of

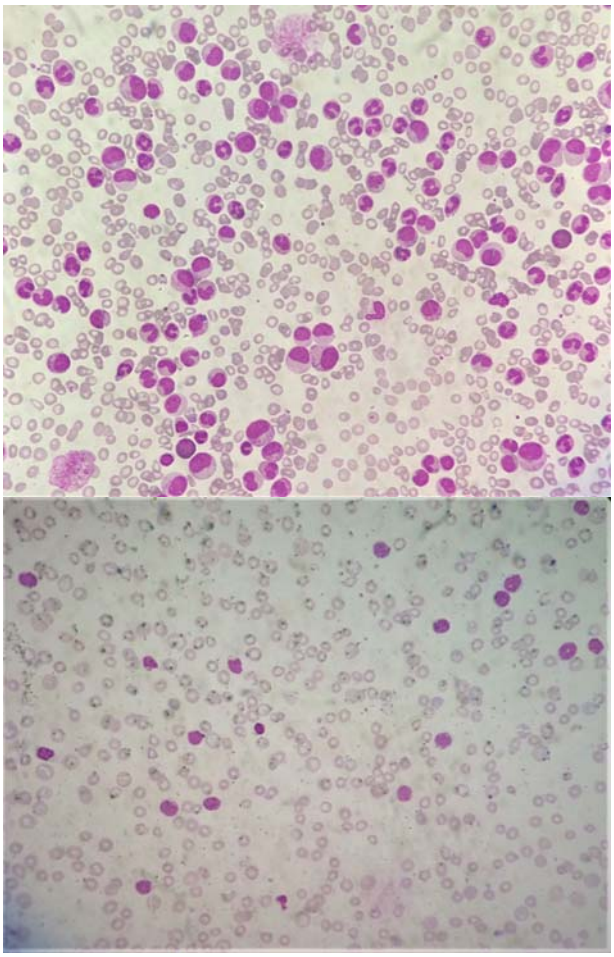

Figure 1.

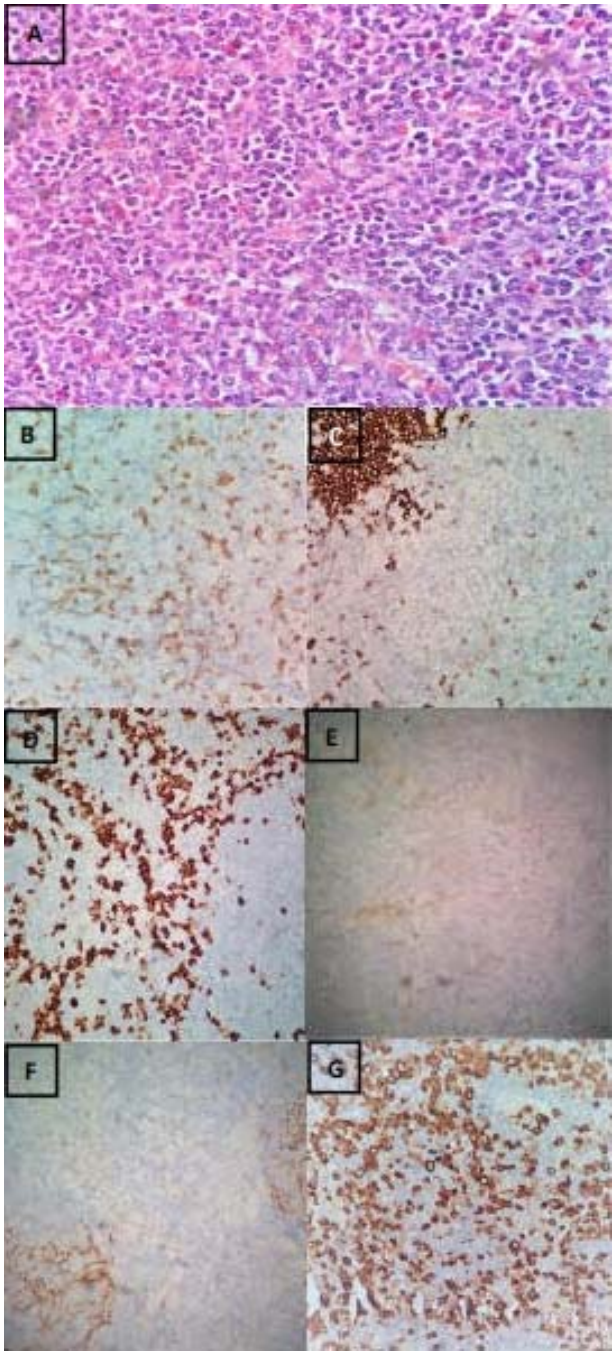

Figure 2.

imatinib therapy. At 2 months the WBC count increased to 22×10^9/L, Hb14 g/dL with PLT 64×10^9/L and blood picture showed 6% blasts. Diagnosis of CML in accelerated phase (AP) was made and patient was started on nilotinib 400mg bd. One month after nilotinib therapy WBC became normal – 6.09×10^9/L, Hb10.4 g/dL, but thrombocytopenia (PLT 38×10^9/L) and peripheral blasts (7%) were persistent. Nilotinib was continued and two weeks later patient readmitted with fever and gum bleeding. Examination revealed a splenomegaly of 13cm and FBC revealed WBC 5.15×10^9/L, absolute neutrophil count 0.02×10^9/L, Hb10.2 g/dL and PLT 6×10^9/L. His coagulation screen was normal. Blood picture showed 45% blasts (Figure 1). Diagnosis of CML in blast phase was made and patient was transferred to Apeksha Hospital, Maharagama for confirmation of the diagnosis and further specific management. Further evaluation of bone marrow aspirate showed 95% of B lymphoblasts confirmed by flowcytometry (CD10-positive, CD19-positive, CD79a-positive, HLA-DR-positive, nTDT-positive). Later patient developed severe pneumonia due to COVID-19 infection and succumbed to the disease a week after the diagnosis of CML in blast phase.

The worldwide annual incidence of CML is 1-2/100 000 population[1]. According to national cancer registry 2015: incidence of CML in Sri Lanka was 139 in both sexes[7]. Untreated CML has a triphasic clinical course: chronic phase, accelerated phase and blast phase[1]. With TKI therapy, progression in to AP is less, therefore, AP has become less important in the management. According to the 5th edition of WHO classification of Haemato-lymphoid tumours, CML is consolidated into 2 phases; chronic and blast phase. Blast phase is defined by ≥20% myeloid blasts in the blood or bone marrow, presence of an extramedullary proliferation of blasts or presence of increased lymphoblasts in peripheral blood or bone marrow[1]. CML commonly is a disease of insidious onset, around 50% are asymptomatic at diagnosis. Symptomatic patients commonly present with constitutional symptoms, anaemia and splenomegaly. There are diverse uncommon clinical presentations in CML including isolated eosinophilia, basophilia, thrombocytosis, generalized lymphadenopathy, hyperviscosity symptoms, bleeding diathesis etc[1]. CML transforms more commonly into AML than ALL (20-30%). Of patients who transform into ALL, B-ALL is commoner than T-ALL. Transformation into mixed phenotype acute leukaemia and NK cell leukaemia are rare[8,9]. Following TKI use CML blast transformation rate is only 1.5% per year[10]. Less than 10% of patients will have extra medullary blast crisis in CML[11]. Lymph nodes are the commonest site of extramedullary blast crisis, and also seen in skin, bones, central nervous system, soft tissues, and para spinal space[11]. Lymphadenopathy in CML is considered a poor prognostic sign[12], and may occur simultaneously or sequentially, thereby posing a significant diagnostic challenge. T-lymphoblast crisis in CML is rare and extramedullary disease is even more rare. In CML, transformation to ALL has a worse prognosis than to AML as it shows poor response to treatment[13]. In CML, lymphadenopathy can be due to extramedullary blast proliferation, extramedullary involvement of cells at different stages of maturation without blasts or drug induced follicular hyperplasia. Rarely there may be co-existing lymphoma. Excision biopsy of lymph nodes is important during evaluation, because there may be alternative diagnosis or advanced disease at presentation even though the bone marrow is in chronic phase. There are several case reports of CML patients in chronic phase in the bone marrow, but having blast proliferation in the lymph nodes. Therefore, lymph node biopsy should be done prior to initiation of treatment. Extramedullary blast proliferation in CML may be present several years before overt blast transformation. Woodson et al. reported a case of lymph node infiltration of myeloblasts one year before bone marrow changes[14]. Prasanna et al. have done a retrospective analysis of 143 patients of CML-CP with different clinical presentations and its effect on prognosis over a 2 year period[12]. Among them 4 had generalized lymphadenopathy (2.8%) and all had p210 transcripts, 2 were EUTOS high risk category. At diagnosis no blast proliferation in lymph nodes were noted and all 4 transformed in to blast phase within a mean time period of 14.5 months. Among the other 139 only one progressed

in to blast crisis[12]. This indicates that patients with lymphadenopathy are at high risk of transformation into CML blast phase. Co-existence of CML and lymphoma is rare with only case reports by way of publications. Both Hodgkin and non-Hodgkin lymphomas have been reported. Starr et al. reported a case of CML with a concurrent diagnosis of follicular lymphoma[4]. Marion et al. reported a case of CML and peripheral T cell lymphoma[6]. Rodler et al. reported a case of blastic mantle cell lymphoma in a CML patient 3 years after the diagnosis of CML[3]. Liu et al. reported a case of CML and classic Hodgkin lymphoma in a young female[5]. Pathogenesis of synchronous multiple malignancies are still not well understood. However, genomic instability in CML during progression of the disease may contribute to the development of lymphoma. Lymphoma can be easily misdiagnosed with CML blast proliferation in lymph node biopsy. Therefore, confirmatory techniques including immunohistochemistry, cytogenetics, flow cytometry, and FISH are required for an accurate diagnosis. There is an entity called Dasatinib associated lymphadenopathy and this may cause lymphadenopathy later in the disease[15].

In conclusion, lymphadenopathy in CML is an uncommon manifestation and indicates high risk of blast transformation. Excision biopsy of lymph nodes are indicated, even if the bone marrow is in chronic phase to exclude extramedullary blast proliferation. Although rare, CML with concurrent lymphoma can be missed and should be excluded by appropriate testing. In patient showing poor response to first line treatment, close monitoring and early escalation of treatment is indicated to prevent progression in to blast crisis. In the TKI era patients with CML die due to causes unrelated to CML. Patients with CML are at high risk of acquiring various infections and appropriate preventive measures should be introduced to minimize mortality. Our patient didn't receive specific ALL chemotherapy due to the covid pneumonia. A better outcome could have been expected if he was able to receive ALL chemotherapy followed by allogeneic bone marrow transplantation.

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