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Case Report

Case report; meta-synchronous triple malignancy in primary diagnosed CML patient

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Abstract: The diagnosis of different types of cancer in a single patient has been appeared in the field in some case reports involving different categories of cancer types either appeared at the same time (synchronous) or subsequently (meta-synchronous). The aim of this report is to present this interesting case of male patient who was under treatment of CML then T-lymphoblastic lymphoma and HCC discovered subsequently. CML, Lymphoma and HCC are arising from different lines of cells with different biology and cytogenetic criteria. CML and acute lymphoblastic leukemia may occur together in cases of blastic crisis of CML. But, they rarely occur together as separate multiple malignancies especially without any history of exposure to ionizing radiation, chemotherapy or transplantation.

Keywords: Chronic myeloid leukemia, T-lymphoblastic lymphoma, hepatocellular carcinoma, hepatitis C virus, tyrosine kinase inhibitor

Introduction

The diagnosis of different types of cancer in a single patient has been appeared in the field in some case reports involving different categories of cancer types either appeared at the same time (synchronous) or subsequently (meta-synchronous).

The aim of this report is to present this interesting case of male patient who was under treatment of CML then T-lymphoblastic lymphoma and HCC discovered subsequently. CML, Lymphoma and HCC are arising from different lines of cells with different biology and cytogenetic criteria. CML and acute lymphoblastic leukemia may occur together in cases of blastic crisis of CML. But, they rarely occur together as separate multiple malignancies especially without any history of exposure to ionizing radiation, chemotherapy or transplantation.

Case report

A 57 years old male was presented to Hematology outpatient clinic since 2014 complaining of left hypochondrial dragging pain and huge splenomegaly by examination. He was diabetic (type II DM) and seropositive hepatitis C confirmed by PCR = 547,714 IU/ml (moderate viremia). Abdominal US revealed Cirrhotic liver with no focal lesions and huge spleen. Laboratory investigations showed WBC = $296*10^9$ with premature myeloid series (shift to left, blasts 3% and basophils 9%), HB = 12.1 mg/dl, Platelet = $341*10^9$, ALT = 39 IU/L, AST = 77 IU/L, total bilirubin = 1.2 mg/dl, serum albumin = 4.3 mg/dl, Blood film coupled with BMA, biopsy and RT PCR (BCR/ABL 1) confirm the diagnosis of CML (Chronic phase), intermediate risk according to Sokal scoring system. He received Imatinib 400 mg 1st line, 3 month re-assessment PCR (BCR/ABL1) was 47%, so he was shifted to Nilotinib 400 mg bid. It was interrupted due to progressive cytopenia, 3 month re-assessment PCR (BCR/ABL1) was 98%. BMA and biopsy revealed hypercellular with no abnormal infiltration by blasts or other abnormal cells. T315I mutation status was negative. Then he started (Dasatinib 100 mg) but he couldn't tolerate its side effects including se-

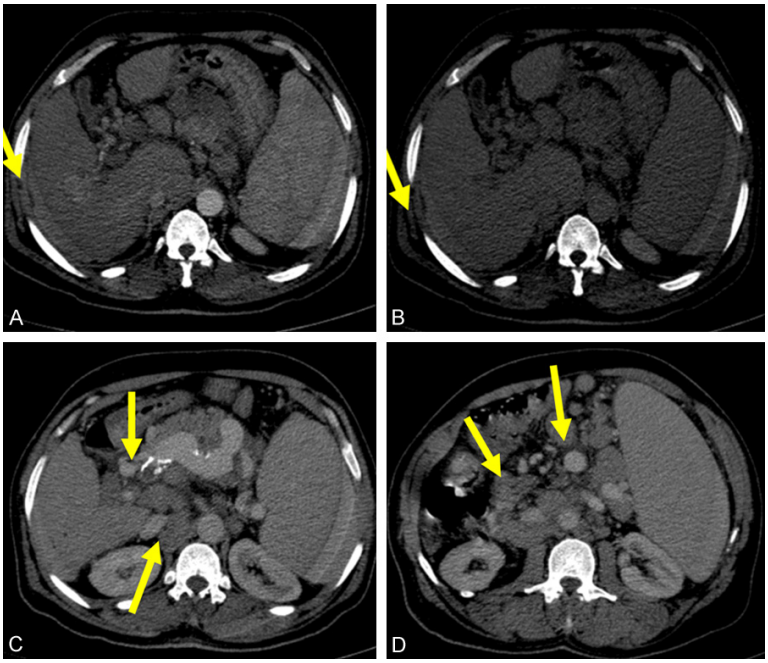

Figure 1. Triphasic MDCT scan of the abdomen and pelvis revealed segment V hepatic focal lesion (yellow arrow) with characteristic pattern of hepatocellular carcinoma (HCC). The lesion shows enhancement in arterial phase (A) and washout in delayed phase (B). Triphasic MDCT scan of the abdomen and pelvis Portal phase (C and D) shows multiple abdominal lymphadenopathies (yellow arrows).

vere abdominal pain with persistent vomiting and diarrhea with evident pancytopenia, then the patient maintained on pegylated Interferon and hydoxyurea.

In February, 2019 he presented by generalized lymphadenopathy with abdominal pain, Abdominal US showed hepatic focal lesions without ascites and superficial US on Lymph nodes showed suspicious criteria. Tri-phasic CT abdomen showed the classical pattern of HCC (**Figure 1**) with portal vein thrombosis and alpha FP >1200 IU/ml with malignant abdominal lymph nodes in para-aortic and inguinal regions with minimal ascites as in (**Figure 1**).

Excisional biopsy from cervical lymph node revealed a picture of acute T-lymphoblastic lymphoma confirmed by positivity of CD99, CD34, CD3, CD5 and TdT. Ki67 proliferation index >90% as shown in (**Figure 2**) and FISH t(9; 22) on this Lymph node biopsy was negative excluding extra-medullary blastic transformation.

After confirming the diagnosis of the triple malignancies, he was planned for best supportive care due to advanced stages of each malignancy. As CML was refractory and last BCR/ABL1 evaluation was 87%, HCC was with portal vein thrombosis and progressive ascites, so, was not fit for Trans-arterial chemoembolization (TACE) and T-Lymphoblastic lymphoma was stage IV and the patient's performance wasn't tolerating aggressive chemotherapy.

Discussion

The multiple primary neoplasms was classified by North American Association of Central Cancer Registries (NAACCR) and the Surveillance Epidemiology and End Results Program (SEER) into two types; Synchronous, in which the cancers occur at the same time or within two months interval and Meta-synchronous, in which the cancers follow each other with more than two months interval [1].

It is important to differentiate if those neoplasms are truly primary or they are secondary to each other. So, the diagnosis of multiple primary malignancies requires specific criteria according to Warren and Gates criteria which include; definite diagnosis of each type of cancer, histo-pathological confirmation and exclusion that one cancer may form the metastasis or the crisis of another [2].

There are few case reports about co-occurrence of lymphoma with myeloid neoplasms, there were two case reports studied by Fu X et al., 2018 about T-LBL with CML and the criteria of the selected patient was close to our patient as their median age was 43 years old and they were both males, but they discovered synchronously [3], also, there were two case reports have been published before in 2016 by Shen ZL et al., both were males, was aged 50 and 80 years old and diagnosed as B-type non Hodgkin lymphoma (NHL) with CML [4] and in 2012 by Wan DM., [5]. The cases were com-

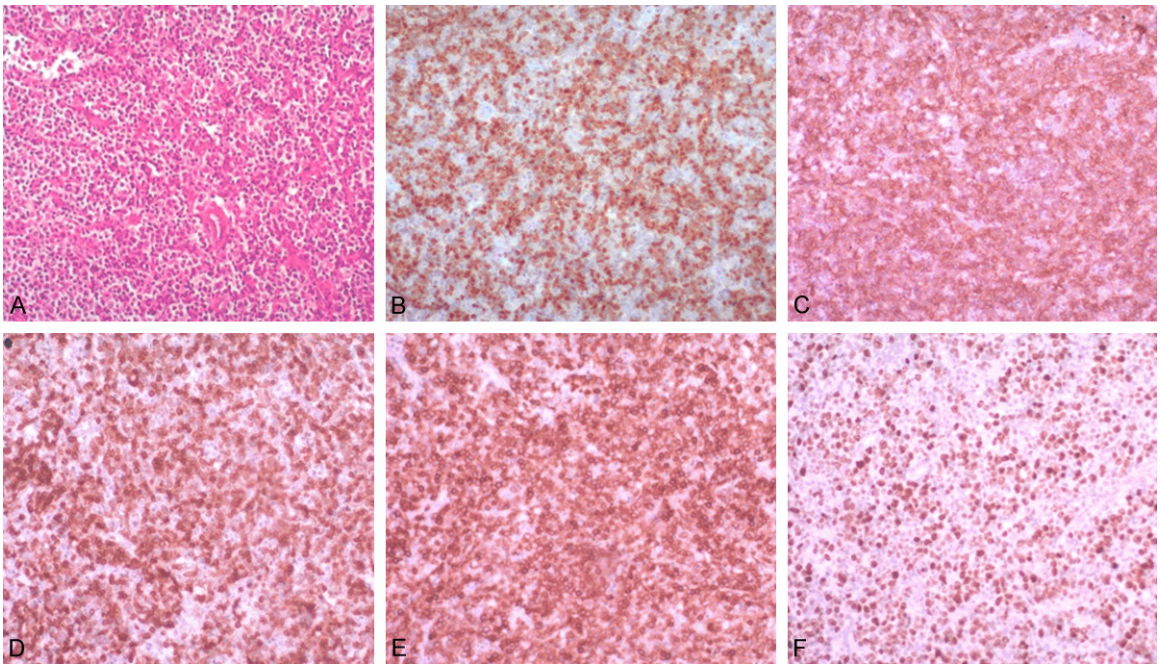

Figure 2. A. Effacement of nodal architecture with diffuse proliferation of small to medium sized cells, with minimal cytoplasm, irregular nuclear contours and frequent mitotic figures (×100). B. Positive nuclear staining of the neoplastic cells for TDT (×100). C. Positive membranous staining of the neoplastic cell for CD99 (×100). D. Positive staining of the neoplastic cells for CD3 (×100). E. Positive staining of the neoplastic cells for CD5 (×100). F. Positive nuclear staining for Ki67 in 90% of the neoplastic cells (×100).

monly characterized by the following according to the available data, they occurred in old age patients with male predominance, prolonged hospital admission due to high tumor burden. It is noticed statistically that Concurrent T-cell lymphoma is more common than B-cell lymphoma with myeloid neoplasms [3].

Relation between HCC and myeloid neoplasm remains unclear. However, there are some reports about relation between HCC and lymphoid malignancies. Kataoka et al., 2006 described a case with concomitant HCC and B-Cell NHL in a patient with nodular regenerative hyperplasia without previous viral infection [6]. However, there is a significant association between HCC and HCV infection and a high prevalence of anti-HCV anti-bodies in patients with NHL, but they mainly correlate HCV with B-cell not T-cell lymphoma and refer that to the chronic stimulation of HCV virus of the immune system mainly B-lymphocytes [7].

There are some researches for detection incidence of secondary malignancies in cases of CML under tyrosine kinase inhibitor (TKI) treatment. Sasaki et al., 2019 found that the incidence of 2ry malignancies as GIT, genito-urinary system, respiratory system malignancies increased in the studied group over about 14 years follow up by 21%, 22% and 15%, respectively, with no relation to specific TKI [8]. Also, Kumar et al., 2018, concluded that the risk of secondary malignancies increased in male patients with CML with an absolute excess risk 1.3% per year compared to matched general population [9].

The pathogenesis of this correlation is not clearly known till now. However, some studies refer the correlation between myeloid and lymphoid malignancies to some possible scenarios. One of them is the immune suppression occurred in patients with T-cell lymphoma/leukemia. Other scenario was response to growth factors released by abnormal T-cells as M-CSF and G-CSF which stimulate growth of myeloid neoplasm as reported by Tsukasaki [10]. Another different scenario has been reported by Chang [11], that FIP1L1-PDGFA is included in the differentiation and progression of both types of neoplasm either myeloid or lymphoid [11].

There is no general agreement was put for management of such cases due to their limited

number. TKI use in CML reduces need for hematopoietic stem cell transplantation (HSCT) apart from cases in blastic crisis or refractoriness to treatment. While as regard T-LBL, Allogenic BMT is considered after reaching complete remission by chemotherapy. Some studies concluded that bi-lineage or tri-lineage hematological malignancies better to be treated by chemotherapy then BMT [3]. Some clinical trials are in progress as use of immunotherapies like Bi-specific anti-bodies which stimulate T-lymphocytes and natural killer cells against tumor cells, targeting two different signals and may help in treatment of bi-lineage neoplasms [12].

Conclusion

Triple malignancy is very uncommon event to occur but it had been reported before in different primary tumor types and sites. Literatures reported increased risk of secondary malignancies in CML patients and some studies focused on the role of TKIs and HCV in their occurrence. So, it will be an interested area for research.

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Disclosure of conflict of interest

None.

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