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Case Report

Therapy Related Chronic Myeloid Leukemia (trCML) or non-Therapy Related Second Malignancy Chronic Myeloid Leukemia (smCML) following Diffuse Large B-Cell Lymphoma(DLBCL): A Case Report and Review of Literature

Robert Louis[1*], Sunil Kumar Gupta[1], Sonal Jain[2], Anurag Mehta[2], and Mohit Agarwal[1]

[1] Deparment of Medical Oncology Unit II, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

[2] Department of Lab Services & Pathology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Abstract

Introduction: Second malignancy could be either previous therapy related or non-therapy related like syndromic or shared etiologic exposure. It could be either a hematological/solid malignancy following tretment for previous solid tumour or prior hematological malignanacy.Review of literature regarding secondary Chronic Myeloid Leukemia (CML) following previous active treatment for primary cancer is listed out for further understanding.

Presentation of Case: We describe a 71 year old elderly male who developed Chronic Myeloid Leukemia(CML) after a period of 6 years during follow up of Stage IV Diffuse Large B-Cell Lymphoma(DLBCL) for which he received 8 cycles of R-CHOP based Chemo-immunotherapy in 2008 .Whether it is therapy related Chronic Myeloid Leukemia (trCML) following prior cytotoxic treatment or simply a non-therapy related second malignancy hronic Myeloid Leukemia(smCML) is a matter of debate.However our patient responded dramatically like denova CML to imatinib therapy.

Conclusion: Therapy related CML or non therapy related second malignancy CML following DLBCL treatment is rare but responds dramatically like denova CML to imatinib therapy.

Keywords: Therapy-related CML; Second malignancy CML; CML following DLBCL treatment

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***Correspondence to:** A. Robert Louis, Deparment of Medical Oncology Unit II, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

E-mail: drrobertlouis@gmail.com

Introduction

Second malignancy could be either previous therapy related or non-therapy related like syndromic or shared etiologic exposure. It could be either a hematological/solid malignancy following treatment for previous solid tumour or prior hematological malignanacy. Review of literature regarding secondary Chronic Myeloid Leukemia (CML) following previous active treatment for primary cancer is listed out for further understanding.

Case Presentation

Seventy one year old male was diagnosed with Diffuse Large B-Cell Lymphoma(DLBCL,Stage IV A) in 2008 (Figure 1)and subsequently treated with 8 cycles of R CHOP . He attained complete metabolic remission and was on regular follow up on outpatient basis. He was completely asymptomatic and his Total leukocyte count(TLC) rose from 18,000/cumm in May 2014 to 87,400/cumm in Aug 2014. The Peripheral smear(Figure 2) showed marked leucocytosis with shift to left with preponderance of myeloid precursors with peak in neutrophil lineage with basophilia (DLC : My-21, MMy-11, N-51,L-05,M-03, E-04,B-05) . A Bone marrow aspirate and Bone marrow biopsy examination along with testing for Bcr/Abl rearrangement was advised. However, he defaulted briefy and returned again with weakness & easy fatiguability and TLC of 2,15,700/cumm in may 2015 with a Differential Count as follows (DLC-Bl-02, My-40, MMy-12,N-40, L-02, M-01, E-01, B-02). Clinical examination revealed no palpable lymphadenopathy or hepatosplenomegaly. RT-PCR for Bcr/Abl rearrangement was done and was positive (Figure 3) . CT scan evaluation showed no evidence of lymphoma involvement. A diagnosis of therapy related Chronic Myeloid Leukemia (trCML) or non-therapy related second malignancy Chronic Myeloid Leukemia (smCML) following DLBCL has been made and started on Imatinib 400 mg once daily with adequate hydration and tumour lysis prophylaxis. He improved dramatically and his last TLC count after one month of imatinib therapy has reduced to 24,000 with marked improvement in weakness and fatigue.

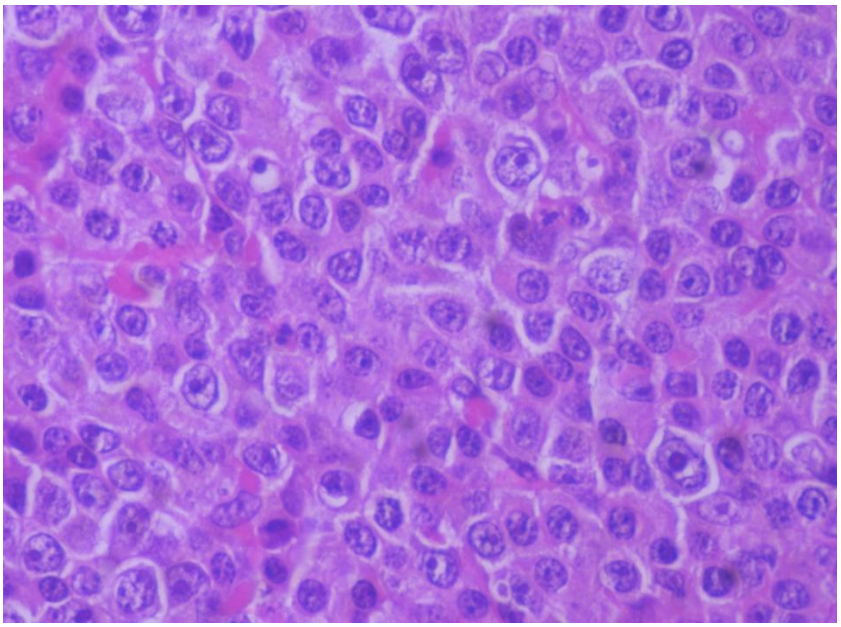

Figure 1 Biopsy of Lymph node showing large monomorphic cells with prominent nucleoli suggestive of Diffuse Large Cell Lymphoma (400X)

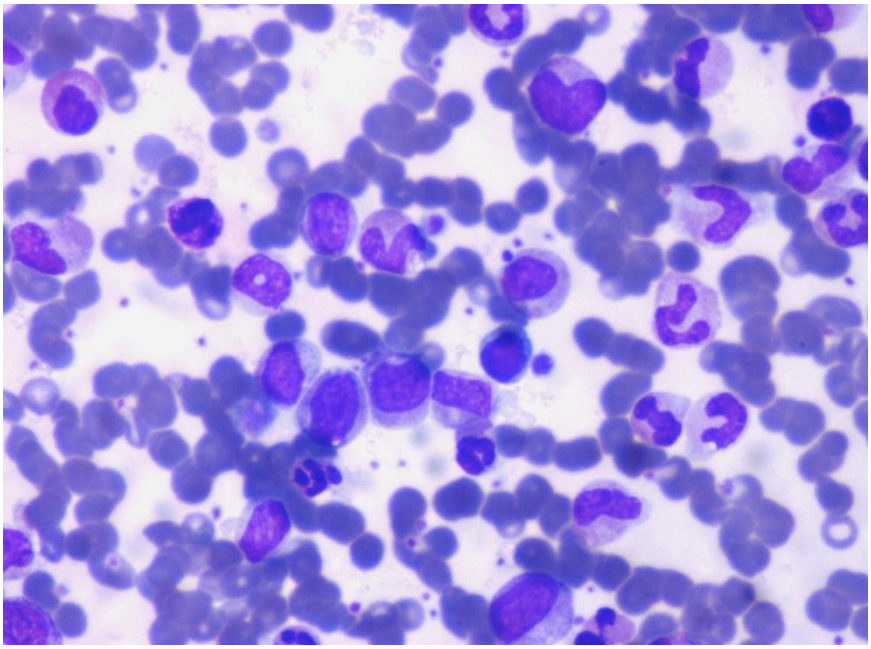

Figure 2 Peripheral smear picture showing left shift in myeloid series with basophils suggestive of Chronic Myeloid Leukemia

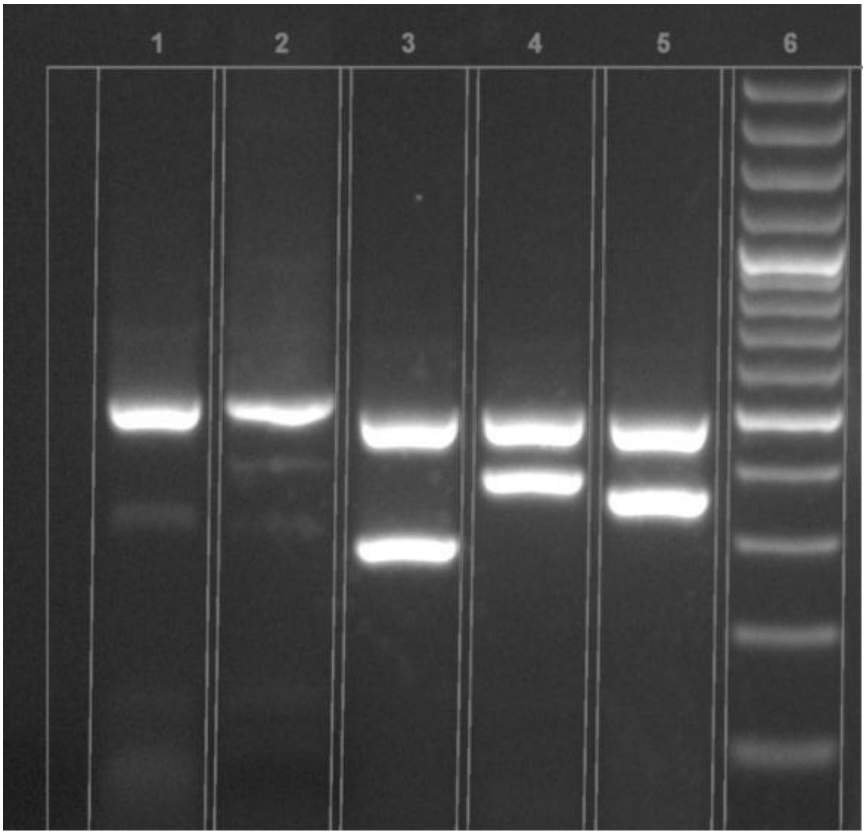

Figure 3 Agarose Gel Detection of Bcr/Abl :Lane1- normal control, Lane 3 patient – Mbcr, Lane 4, 5 - +ve control, Lane 6 – 100bp molecular ladder, E1a2 – 381bp, E13a2 – 285bp, E14a2 – 360bp

Discussion

Non-Hodgkins Lymphoma(NHL) patients have a significant increased risk of developing second primary cancers. Second malignancy following non-Hodgkins lymphoma(NHL) therapy can be either therapy related or non-therapy related. Therapy related factors include previous chemotherapy(Topisomerase inhibitors, alkylationg agents etc), Radiation therapy or combined modality treatment. Factors such as better survival following previous effective treatment, increasing age, genetic susceptibility, viral infections, tobacco use or immunolgic alteration are possible reasons for non-therapy related second malignancy[1-3]. The risk of second cancer after NHL increases as much as 47% and the incidence ratio increases with age with the cumlulative incidence of 8.2% at 15 years [4,5]. The pooled Relative Risk of second malignant neoplasms after NHL therapy is increased than general population and the risk impact differs for various treatment modalities [6]. Therapy related second primary cancer increases with every decade since NHL diagnosis with relatively excess risk observed in older patients [7,8]. The pattern of second malignancy differs by NHL subtype. Both hematological and solid malignancy has been documented after NHL therapy. Treatment related malignancy following NHL therapy include cancer of lung, bladder, stomach, myeloid leukemia and hodgkins lymphoma. While the Standardised Incidenced Ratio(SIR) of acute non-lymphocytic leukemia(SIR 4.96 & 5.96) is increased enormously after Diffuse large B Cell Lymphoma (DLBCL) and Follicular Lymphoma(FL) treatment, Chronic Myeloid Leukemia(SIR 2.5 vs 0.9 & 1.75) risk is elevated after DLBCL as compared with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia and Follicular Lymphoma treatment($P < 0.5$) [9]. Around 150 cases of therapy related or second malignancy CML has been described in literature post treatment of solid or Lymphoid malignancies(Table 1).The median duration in development of trCML is 4 years(range 5 months to 14 years).Therapy related CML has been described after the receipt of chemotherapy or Radiotherapy alone or after combined modality treatment.Prior therapy for hematolymphoid malignancies for low grade NHL (like CLL, follicular lymphoma, waldenstroms macroglobulinemia) and high grade NHL(like DLBCL) included treatment with chlorambucil to Rituximab based immunochemotherapy with or without Radiotherapy [10-26]. Therapy for solid tumours with histologic specific chemotherapy schedules (including oxaliplatin, irinotecan, 5Flurouracil based therapy for colorectal cancer[27-31] and anthracyclin based chemotherapy for breast cancer) and Radiation therapy for solid tumours (like cancer cervix, breast cancer, rectal cancer) [32-35] as a part of multimodality treatment has caused trCML. Radioactive therapy with 131I for thyroid cancer has also been implicated in therapy related CML [36-38]. Recently more cases of treatment related CML has been noted after using S1 chemotherapy especially when given for prolonged time(typically 1 or 2 yrs) as in Japan where S1 is being used increasingly in many solid tumours in adjuvant or metastatic setting [39-44]. Two patient had unusual synchronus presentation of CML with Gastrointestinal Stromal tumour diagnosis which has been treated with imatinib, the standard treatment for both the condition with good outcome [45]. Treatment related CML or non therapy related second malignant CML cannot be distinguished from denova CML cytogenitically. Treatment related CML is more increasingly recognised than non-therapy related second malignant CML because of increasingly aggressive therapy for primary malignancy although there is no better objective way to identify the nature of them. Non therapy related Second malignant CML tend to increase with increasing age at onset of first primary and is a rare entity [13,14]. However both therapy related or non-therapy related CML respond favourably to imatinib therapy and behave similar to denova CML [21,22].

Secondary CML following DLBCL has been reported recently in 4 case reports where it was noted

to occur from 9 months to 10 year post DLBCL treatment with CHOP based chemotherapy plus or minus rituximab /Radiotherapy [10,12,15,19]. One case diagnosed CML synchronously with NHL relapse which was treated with combination of rituximab and Imatinib [18].

Table 1 Table showing published Case reports/Series of therapy related or second malignancy CML following treatment of primary hematolymphoid or solid tumours.

Author	Primary Cancer	Treatment	Number of patients	Duration since primary treatment	Reference
Demiriz IŞ	DLBCL	R CHOP	1	5 years	10
Shibazaki M	Folicular Lymphoma	Chemotherapy(RFM Protocol)	1	3 years	11
Lee HY	DLBCL	Chemotherapy(CHOP)+Radiation	1	10 years	12
Aguiar RC	Both solid and hematologial(5 CLL,2 NHL)	Chemotherapy	32	-	13
Specchia G	Both solid and hematologial	-	9+77(therapy related)	-	14
Zahra K	DLBCL in a child	Chemotherapy	1	9 months	15
Alsop S	ALK +ALCL	Chemotherapy	1	4 years	16
Bolaños-Meade	Lymphoid	Chemotherapy	1	7 years	17
Breccia M	NHL	chemotherapy	1	-	18
Hsiao HH	Lymphoma(High grade MALT)	Chemotherapy+PBSCT	1	10 months	19
Wandroo FA	Hairy cell leukemia	deoxycoformycin	1	4 years	20
Ramanarayanan J	Lymphoid malignancies(HL,NHL,CLL)	Chemotherapy	3	8,10,2.5 years respectively	21
Waldman D	NHL,Nasopharynx	Chemotherapy,Radiation	2	-	22
Verhoef GE	Hodgkins lymphoma	Chemotherapy	1	8 years	23
Cazzola M	NHL	Chemotherapy+Radiotherapy	1	-	24
Ragupathi L	Multiple myeloma	Steroids	1	1.5 years	25
Majado MJ	Waldenstrms macroglobulinemia	Chlorambucil	1	3 years	26
Gokel Y	Colon adenocarcinoma	Chemotherapy(cisplatin+5FU)	1	-	27
Vakili-Sadeghi M	Rectosigmoid	Oxaliplatin +5FU	1	2 years	28
Kadikoylu G	Rectal adenocarcinoma	Chemotherapy(Oxaliplatin,5	1	3 years	29

		FU,Irinotecan)			
Buxhofer-Ausch V	Metastatic colorectal cancer	Chemotherapy(FOLFIRI +Cetuximab)	1	1 year	30
Manabe M	Rectal cancer	S1 therapy(1 year)	1	3 years	31
Pavithran K	Papillary thyroid caner	Radioactive iodine 131	1	14 years	32
Wang KL	Papillary thyroid cancer	Radioactive iodine 131	1	13 years	33
Walgraeve D	Thyroid cancer	Radioactive iodine 131	1	-	34
Shimon I	Papillary & Follicular	Radioactive iodine 131	2	4 & 10 years	35
Porta C	Breast cancer	Chemotherapy	1	-	36
Bauduer F	Breast,cervix	Radiotherapy	3	1-25 years	37
Abu-Ghanem S	Breast cancer	Chemotherapy	2	1 year	38
Tsuzuki M	Gastric cancer	5'-deoxy-5-fluorouridine	1	6 years	39
Higuchi M	Gastric cancer	T –S1 therapy(21 months)	1	3 years	40
Waller CF	Small cell lung cancer	High dose chemotherapy+autoSCT+Radiotherapy	1	2 years	41
Noda M	Pineal germinoma	Chemotherapy+Radiation	1	4 years	42
Numata A	Ewings sarcoma	Autologous stem cell transplant	1	4 years	43
Langabeer SE	Prostate cancer	Radiotherapy	1	5 months post RT	44
Sakamoto E	GIST	Imatinib	2	synchronus	45
Present Case	DLBCL	R-CHOP	1	6 years	-

Conclusion

In our patient, the secondary CML is believed to be either treatment related or non therapy related. The fact he has received prior rituximab and anthracycline based therapy and no clinically palpable or enlarged splenomegaly by imaging may point to therapy related CML. The older age at onset of primary NHL and development of CML after 6 years of follow up may indicate non therapy related secondary CML, although such factors and other unknown factors in play cannot be identified clinically to distinguish accurately between the two. Therapy related CML or non therapy related second malignancy CML following DLBCL treatment is rare but responds dramatically like denova CML to imatinib therapy.

Consent

We conform Informed written consent from the patient has been obtained for the purpose f publication of case report.

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