A case report of primary cutaneous diffuse large B-cell lymphoma in chronic myeloid leukemia after treatment with dasatinib

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Key words: chronic myeloid leukemia; dasatinib; primary cutaneous diffuse large B-cell lymphoma.

INTRODUCTION

Tyrosine kinase inhibitors (TKIs), the standard treatment for chronic myeloid leukemia (CML), improved the outcome of CML and have been the focus of research for more effective treatments. Imatinib emerged as the first TKI to be approved by the Food and Drug Administration. Dasatinib, a second-generation TKI, is known to have 100- to 300-fold higher activity than imatinib and is superior to imatinib in achieving a major molecular response in treatment-naïve patients with CML.[1] Therefore, more physicians are choosing dasatinib as the first line agent for CML. However, concerns have been raised regarding their side effects, particularly the potential development of hematological malignancies. Here, we report a case of primary cutaneous diffuse large B-cell lymphoma that developed during CML treatment with dasatinib. To the best of our knowledge, this is the first report of primary cutaneous diffuse large B-cell lymphoma during CML treatment with dasatinib.

Abbreviations used:

CD: cluster of differentiation
CML: chronic myeloid leukemia
EBV: Epstein-Barr virus
TKI: tyrosine kinase inhibitors

CASE REPORT

A 63-year-old woman presented with multiple painful erythematous nodular lesions that had appeared on her face and scalp 3 months prior. She had been diagnosed with CML 5 years prior (December 2018) and achieved a complete hematologic response 7 months after starting treatment with dasatinib daily 100 mg. She had been taking a daily dose of 80-mg dasatinib for approximately 2.5 years. However, in February 2022, mild pulmonary hypertension accompanied by pericardial effusion was confirmed, and the dose of dasatinib was reduced to 40 mg/d. In November 2022, a massive pericardial effusion and bilateral pleural effusion were discovered. Despite the use of diuretics along with multiple thoracenteses, adequate control of effusions and associated dyspnea and chest pain was not achieved. Therefore, dasatinib was permanently discontinued in late November 2022 and after a 2-month break, CML treatment was resumed with imatinib 300 mg daily from January 2023. The patient first discovered nodular skin lesions on scalp around the end of December 2022 and multiple new lesions subsequently appeared on face. Dermatological examination revealed multiple firm erythematous plaques of various sizes. Some lesions exhibited central necrosis and ulceration with crusting (Fig 1). A skin biopsy was performed on the right postauricular lesion, and histological examination revealed diffuse infiltration of the dermis by large atypical lymphoid cells that were medium to large in size, round to

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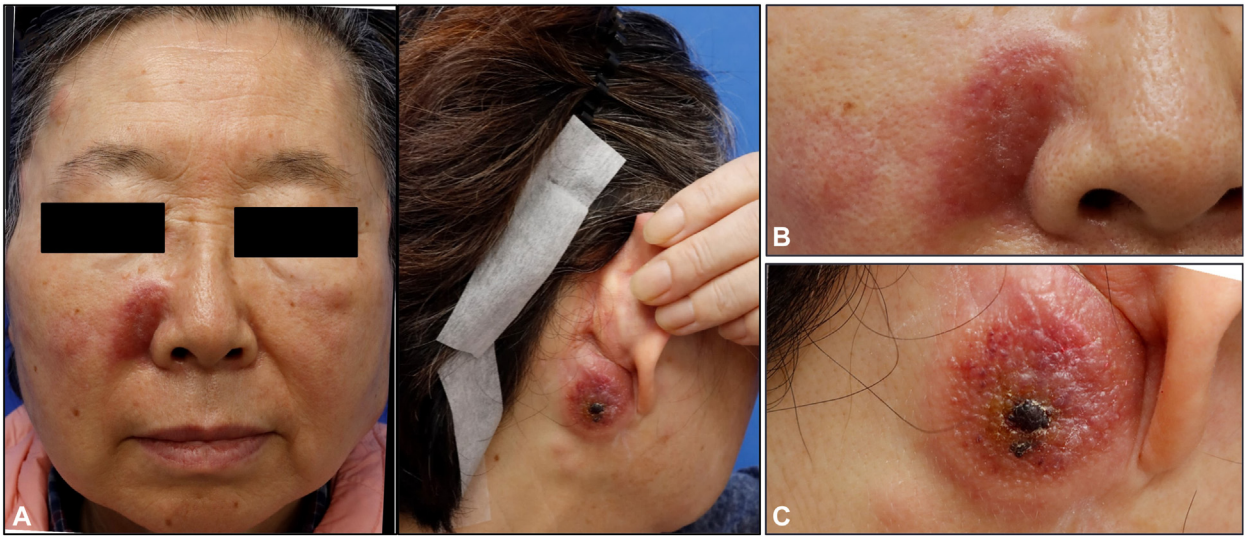

Fig 1. **A,** Multiple firm erythematous to violaceous plaques of various sizes on face and scalp. **B,** Closed up view; well demarcated oval shape plaque on *right* nasolabial fold. **C,** Closed up view; central necrosis and ulceration with crusting were observed in right posterior auricular area.

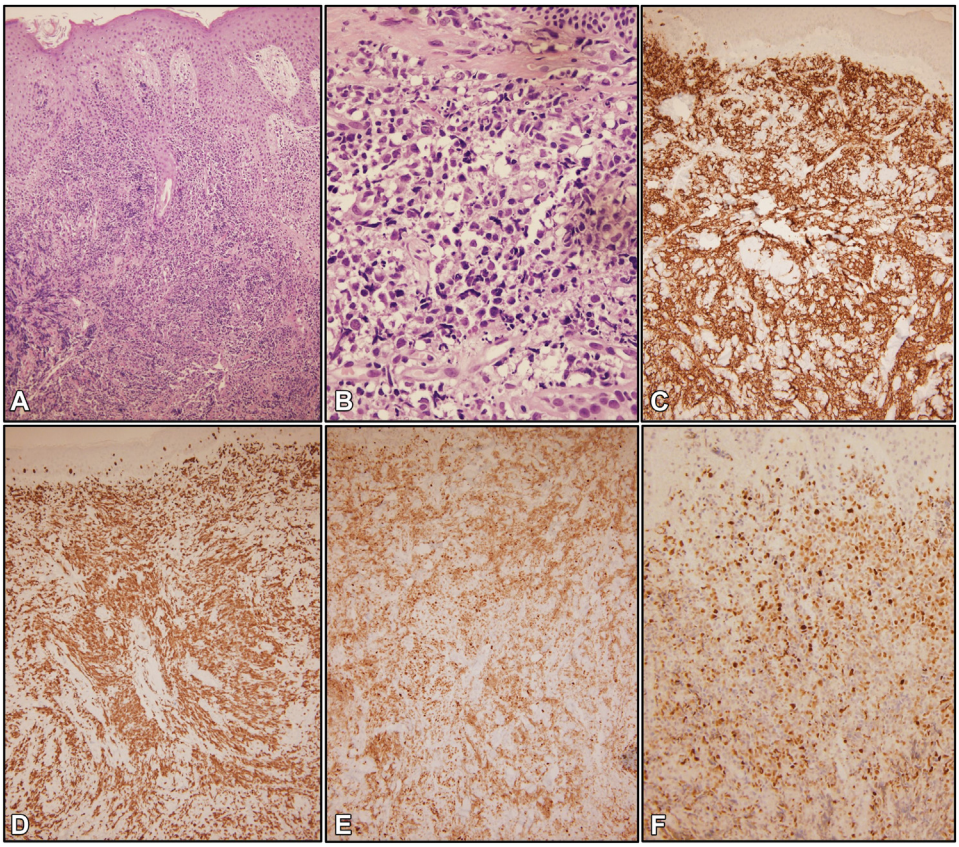

Fig 2. Histopathological findings of right postauricular lesion. H&E staining showed diffuse infiltration of dermis by large atypical lymphoid cells (**A,** hematoxylin and eosin ×50; **B,** hematoxylin and eosin ×400). Immunohistochemical staining was positive for (**C**) CD 20, (**D**) Ki-67(>90%), (**E**) Bcl-6, (**F**) MUM1.

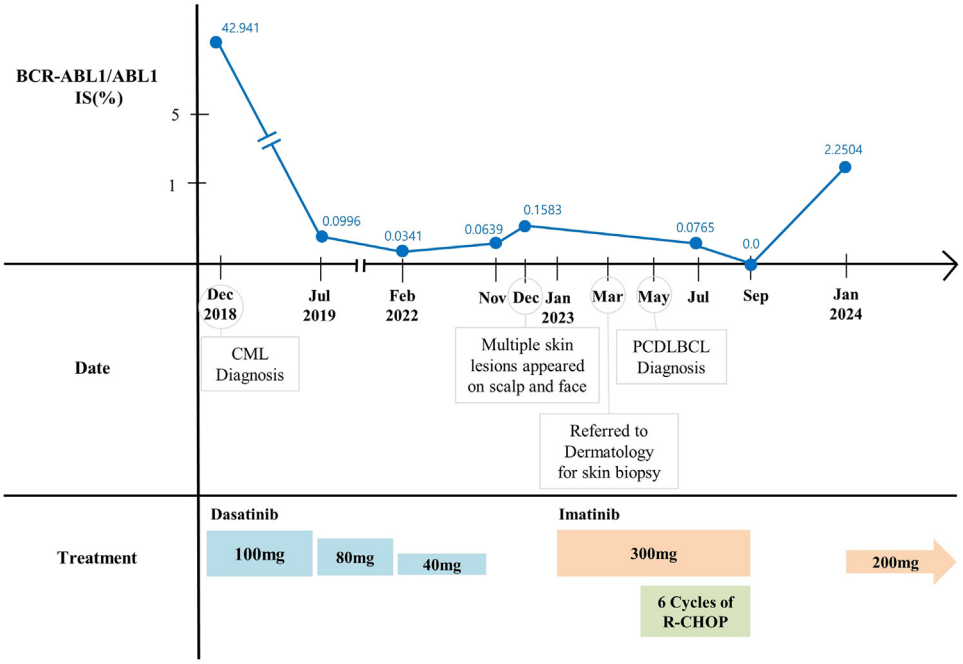

Fig 3. Timeline of the clinical course, laboratory findings, and management in the present patient. *CML*, Chronic myeloid leukemia; *PCDLBCL*, primary cutaneous diffuse large B-cell lymphoma; *R-CHOP*, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

oval-shaped nuclei exhibiting fine chromatin, and eosinophilic nucleoli with a pale cytoplasm. Immunohistochemical analysis showed a positive reaction for cluster of differentiation (CD) 19, CD 20, CD 10, MUM-1, Bcl-6, and Bcl-2 (focal weakly) of the atypical lymphocytes. The Ki-67 proliferation index was over 90%. However, CD 3, cyclin D1, CD 34, c-kit, myeloperoxidase, and TdT showed negative reactivity (Fig 2). Bcl-6 rearrangements were detected using fluorescence in situ hybridization; however, neither Bcl-2 nor c-MYC rearrangements were detected. Epstein-Barr virus (EBV) in situ hybridization result was negative. Positron emission tomography showed no evidence of extracutaneous lymphoma involvement. Finally, the diagnosis of primary cutaneous diffuse large B-cell lymphoma was obtained. After 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, a complete remission was confirmed. For CML, imatinib was discontinued in September 2023 when BCR-ABL1 transcript copies were undetectable in real-time quantitative reverse transcription polymerase chain reaction. However, in January 2024, owing to elevated BCR-ABL1 transcript copy levels, imatinib was restarted and continued at 200 mg per day. The timeline of clinical course, laboratory results, and management are shown in Fig 3.

DISCUSSION

Although the risk of secondary malignancies due to TKIs has long been controversial, an increasing number of case reports and studies have shown an increased risk of secondary malignancies in patients with CML receiving TKIs. It has been reported that secondary malignancies develop in 3.1% to 4.5% of patients with CML during treatment, of which lymphoma accounts for approximately 5%.[2-4] The mechanism of the development of hematological malignancies in patients with CML with TKI therapy has not been completely elucidated. Takakuwa et al have suggested 'TKI-induced immunosuppression' as one possible hypothesis.[5] TKIs are known to hinder the function of T, B, and NK cells, which may reduce immunity and contribute to the development of hematologic neoplasms. However, Paola et al found a higher incidence of second malignant neoplasms in CML patients with CML before introduction of TKIs, which may indicate that CML itself is a direct risk factor for secondary malignancies.[6] Fabarius et al reported that the unstable function of stem progenitor cells due to chromosome mutations in CML remains a high-risk factor for carcinogenesis.[7] Another possible risk factor is EBV. EBV makes immunocompromised patients susceptible to the B-cell lymphoproliferative disorders due to the

Table I. Reported cases of lymphomas that developed during or after TKI treatment in patients with CML

Case	Age /Sex	TKIs	Symptoms	Interval (Months)	Diagnosis	Treatment	Prognosis	Author
1	65/M	Imatinib	- Anorexia - Weight loss	10	MCL	CHOP x5	Died	Rodler et al.[8]
2	53/F	Imatinib	- Swelling of parotid gland	84	EMZBCL	Anthracycline	CR	Mihaylov et al.[9]
3	50/M	Imatinib	- No symptom	36	FL	Rituximab	CR	Fujiwara et al.[10]
4	50/M	Imatinib Dasatinib	- Fever - Pleural effusion with hilar lymphadenopathy	120	HL	ABVDx6	CR	Gajendra et al.[11]
5	63/M	Imatinib Nilotinib	- Gastric discomfort	84	DLBCL	RCOP, Lenalidomide	CR	Cai et al.[12]
6	8/M	Imatinib Dasatinib	- Cervical lymphadenopathy	45	PTNFL	Not available	NA	DominguezPinila et al.[13]
7	75/M	Imatinib Nilotinib Bosutinib	- Malaise - Posterior neck pain	161	HGBCL	DA-EPOCH-R	CR	Teruhito et al.[5]
8	49/M	Imatinib	- Multiple palpable lymph nodes on neck	72	FL	Bendamustine, Rituximab	CR	Sajad et al.[14]
9	64/M	Imatinib Nilotinib Dasatinib	- Swelling of the neck - Fever - Night sweats	72	HL	AVD x4	CR	Paczkowska et al.[15]
Our case	63/F	Dasatinib	- Multiple painful erythematous plaque on face and scalp	48	PCDLBCL	R-CHOP x6	CR	

The table compares all the cases based on several factors, such as age, sex, types of TKIs used to treat CML, interval between start of TKI, and onset of symptoms, treatment option, and prognosis. *ABVD*, Doxorubicin, bleomycin, vinblastine, and dacarbazine; *AVD*, adriamycin, vinblastine, and dacarbazine; *CML*, chronic myeloid leukemia; *CR*, complete response; *DA-EPOCH-R*, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; *DLBCL*, diffuse large B-cell lymphoma; *EMZBCL*, extranodal mediastinal B-cell lymphoma; *FL*, follicular lymphoma; *HGBCL*, high-grade B-cell lymphoma; *HL*, hodgkin lymphoma; *MCL*, mantle cell lymphoma; *NA*, not available; *PCDLBCL*, primary cutaneous diffuse large B-cell lymphoma; *PTNFL*, pediatric-type nodal follicular lymphoma; *R-CHOP*, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; *RCOP*, rituximab, cyclophosphamide, vincristine, and prednisone; *TKI*, tyrosine kinase inhibitor.

outgrowth of EBV-infected B cells and may particularly contribute to Hodgkin and non-Hodgkin lymphoma development.[5] However, in situ hybridization for the EBV was negative in our patient.

Table I summarizes the detailed clinical course of lymphomas reported in the literature to date that occurred during or after TKI treatment in patients with CML[5,8-15]; All cases are B-cell lineage lymphoma, and imatinib was the most commonly administered drug. Miranda et al also found an increased standardized incidence ratio of non-Hodgkin lymphomas after imatinib treatment in a long-term observational study of patients with CML.[16] However, to date, there have been only a few cases of lymphoma occurring after dasatinib administration, and most cases have been reported as effusion-based lymphoma.[17,18] Unlike the other cases in Table I, our case is unique in that the first symptom of lymphoma appeared only as a cutaneous manifestation limited to skin. Dermatologists should be aware that lymphomas may develop after dasatinib treatment, and that the first symptom of lymphoma can present as skin lesions. In addition, further studies are needed to determine whether there is a difference in the incidence rate of lymphoma depending on the type of TKIs, including whether dasatinib actually increases the risk of lymphoma, as imatinib may. Our patient and most of the reported cases in Table I responded well to initial chemotherapy. However, there have been no clear reports on the prognosis and standardized treatment guideline of malignant lymphoma developed during TKI therapy. Currently, treatments for TKI-associated lymphomas are the same as those for de novo lymphomas.[5] Therefore, larger data sets are needed to better establish the relationship between lymphoma and TKI treatment, and to suggest treatment directions that ensure long-term safety for patients.

Conflicts of interest

None disclosed.

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