UCLA Health

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Abstract Form

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Project Title:	The Association between Tyrosine Kinase Therapy and the Development of Primary Effusion Lymphoma in an HIV-negative Patient

Research Category (please check one):

☐	**Original Research**	☒	**Clinical Vignette**	☐	**Quality Improvement**	☐	**Medical Education Innovation**

Abstract

Tyrosine kinase inhibitors (TKI) are small molecule inhibitors of enzymes that catalyze the phosphorylation of tyrosine residues, thereby blocking downstream signal activation of cell proliferation pathways. Since their introduction over 20 years ago, TKIs have revolutionized targeted cancer therapy. Despite their favorable side effect profiles compared to traditional chemotherapy agents, TKIs have unique toxicities due to both on-target and off-target effects, including hand-foot syndrome and colitis. The second-generation drug dasatinib commonly leads to expansion of large granular lymphocytes (LGLs) with anti-leukemic and inflammatory properties, a phenomenon unique among the TKIs. Dasatinib is also the most heavily implicated TKI in the development of pleural effusions, occurring in nearly one third of patients in the landmark DASISION trial. In this vignette, we report the unusual development of an HHV-8 positive primary effusion lymphoma (PEL) in a patient with CML treated with both dasatinib and nilotinib.

A 60-year-old Hispanic man from El Salvador initially presented in December 2017 with a 3-month history of weight loss and night sweats. He was found to have an elevated white blood cell count of 236 with increased myeloid precursors. He underwent a bone marrow biopsy showing 5% myeloblasts, aberrant CD7 and CD56, and a BCR-ABL1 p210 transcript detected at 52.4%. A diagnosis of chronic myeloid leukemia (CML) was made. Due to a high Sokal risk index of 2, the patient was treated with dasatinib 100 milligrams daily. Three years after treatment initiation with dasatinib, he was noted to have an asymptomatic lymphocytosis on his labs. Flow cytometry revealed a clone of large granular lymphocytes. He was subsequently diagnosed with a treatment-related colitis, which resolved with loperamide. In May 2021, he presented with exertional dyspnea and chest discomfort and was found to have large bilateral pleural effusions and a large circumferential pericardial effusion. Cytology from the pleural effusions did not reveal malignant appearing cells and flow cytometry was negative for immunophenotypically abnormal leukocytes. He was treated with thoracentesis and a short course of prednisone for dasatinib-related serositis then switched to nilotinib 300 mg twice daily in June 2021. The patient returned to the Emergency Department in January 2022 with recurrent dyspnea on exertion. A CT thorax demonstrated an increase in size and complexity of his left-sided pleural effusion compared to his prior study from May 2021. Cytology from the effusion was notable for large immature appearing mononuclear cells, which stained positive for CD138 and HHV-8, consistent with a diagnosis of PEL. HIV testing was negative. TKI therapy was held over the ensuing three months. As the patient did not have symptomatic effusion recurrence or extra-cavitary disease, chemotherapy for the PEL was deferred. Eventually, nilotinib therapy was resumed for treatment of his CML with close radiographic monitoring of his pleural spaces. As of January 2023, the patient's imaging showed minimal residual left-sided pleural fluid and no extramedullary disease.

PEL in the absence of HIV or another immunocompromised state such as organ transplantation is rare. Patients from HHV-8 endemic regions can develop PEL without an underlying immune deficiency, however, this phenomenon is exceptionally uncommon, and this patient did not hail from an HHV-8 endemic region. Thus, we aim to make clinicians aware of the possible causative relationship between TKI therapy and the development of PEL. To our knowledge, there have been no large-scale investigations into the association between dasatinib or nilotinib and the development of secondary malignancies. Our case study is the first to report an HHV8-positive primary effusion lymphoma associated with the use of TKIs. It is worth noting that despite the aggressive nature of HHV-8 positive PEL and its poor prognosis (median overall survival of 6 months), this patient has done well with only withdrawal of TKI therapy and conservative management. It is unclear whether the patient had PEL during his first occurrence of pleural effusion while on dasatinib or if he developed it later while on nilotinib, as pleural flow cytometry cannot reliably detect malignant cells in PEL. The preceding large granular lymphocytosis and other immune sequelae may support a mechanism of immune dysregulation leading to HHV-8 reactivation as the link between TKI therapy and PEL. The resolution of the LGL clone after dasatinib discontinuation and ongoing remission despite resumption of nilotinib are supportive of dasatinib as the most likely inciting trigger. This case suggests that further investigations should be undertaken to elucidate the relationship between TKI therapy and PEL.