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Tyrosine Kinase Inhibitor Induced Isolated Pericardial Effusion

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Key Words
Tyrosine kinase inhibitor · Pericardial effusion · Leukemia

Abstract
Long-term therapy with tyrosine kinase inhibitors (TKI) has resulted in improved outcomes for patients suffering from Bcr-Abl fusion protein-harboring leukemias. As a result, a growing population of patients on TKI therapy present to their primary care providers. In this case, we report on the case of a 62-year-old male who presented with a symptomatic pericardial effusion. After pericardiocentesis, malignancy and infectious etiologies were excluded. The pericardial effusion was attributed to his TKI, with a transition of this medication to a different TKI. A repeat evaluation 1 month following the withdrawal of the offending agent showed no recurrence of his pericardial effusion on echocardiogram. In this report, we will highlight a rare but important side effect of TKI therapy before discussing its purported mechanisms and differing incidence rates. Early recognition of serosal inflammation related to long-term TKI therapy by primary care providers is important in preventing patient morbidity and mortality.

Introduction

With improved outcomes for patients suffering from Bcr-Abl fusion protein-harboring leukemias [1–4], there is a growing population of patients on long-term therapy with tyrosine kinase inhibitors (TKI) directed at the Bcr-Abl fusion product of the Philadelphia chromosome. While previous TKIs have been associated with pleural effusions, the effect of newer TKIs on the development of serositis is less known. We present a case report of a patient who developed an isolated pericardial effusion after treatment with nilotinib for pre-B cell acute lymphoblastic leukemia (ALL).

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Clinical Case Report

A 62-year-old male with a history of pre-B cell ALL presented to our hospital with a 2- to 3-day history of shortness of breath with exertion. He endorsed a decreasing exercise tolerance and increased lower extremity edema over the previous 2 weeks. He denied chest pain, heart palpitations, neck pain, jaw pain, lightheadedness, dizziness, or sick contacts.

His oncologic history extends back 2 months; at this time he was diagnosed with pre-B cell ALL after a routine lab work showed an abnormal complete blood count with 30,000 white blood cells and 29% blasts. He was initiated on HyperCVAD chemotherapy (consisting of cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate), which was discontinued prior to the end of the first cycle, secondary to acute kidney injury. Based on cytogenetic studies showing the presence of the Philadelphia chromosome, he was started on nilotinib, a second-generation TKI, as an adjunct to chemotherapy. A bone marrow biopsy 1 week prior to presentation following the first cycle of HyperCVAD and 6 weeks of nilotinib therapy showed a mildly hypercellular bone marrow with trilineage hematopoiesis. Pathology, flow cytometry and chromosome studies showed no evidence of leukemia in the bone marrow or peripheral blood.

Upon initial evaluation, he was found to have a regular pulse of 84, a blood pressure of 132/80, a respiratory rate of 20 and nonlabored breathing at rest. His SaO_2 was 100% in room air. His initial exam was significant for clear oropharynx and nares, gray tympanic membranes bilaterally and clear lungs with good air movement. His cardiac exam was notable for muffled S1 and S2 with an S3 at the left lower sternal border and apex, a nondisplaced point of maximum impulse, a jugular venous distension of 17 cm H_2O with sustained hepatojugular reflexes, and a pitting edema extending up to the mid-lower-legs bilaterally. He demonstrated the presence of pulsus paradoxus with a decrease in systolic blood pressure by 15 mm Hg with inspiration. There was no friction rub. His EKG was notable for a new finding of low voltage with electrical alternans (fig. 1, fig. 2). A transthoracic echocardiogram showed a 2.2-cm pericardial effusion during systole with a 2.7-cm effusion during diastole with an early diastolic tamponade physiology (fig. 3). His prior echocardiograms had shown a normal right and left ventricular function without any wall motion abnormalities or evidence of effusion.

He underwent pericardiocentesis with the removal of 450 ml of serosanginous fluid and catheter placement with a subsequent normalization of his EKG (fig. 4). He experienced an additional 100 ml of drainage over the next 24 h and prior to the removal of the catheter. The effusion was bloody with 2,257 white blood cells, 40 polymorphs and 60% mononuclear cells. Cytopathology and flow cytometry revealed no evidence of leukemia. The plasma and pericardial fluid were negative for Epstein-Barr virus, cytomegalovirus, parvovirus B19, enterovirus, and adenovirus via polymerase chain reaction. The pericardial fluid was negative for cryptococcal antigen. Plasma beta-D-glucan, galactomannan, antinuclear antibodies, rapid plasma reagin, histoplasma, and HIV tests were all negative. A nasopharyngeal aspirate respiratory viral panel was negative. Bacterial, fungal, and mycobacterial cultures resulted in no growth from the pericardial fluid.

As the evaluation of the effusion ruled out likely alternative etiologies, it was attributed to the patient's TKI, nilotinib. This medication was transitioned to bosutinib and he underwent a repeat transthoracic echocardiogram 1 month after discharge, noting the presence of only a trace of pericardial effusion. At that time, his symptoms of dyspnea on exertion had resolved and he showed no evidence of jugular-venous distention, pulsus paradoxus, hepatojugular reflux, or lower extremity edema.

Discussion

In the era of targeted therapy and personalized medicine, the development of therapies aimed at the inhibition of disease-specific pathways has led to a widespread use of TKIs. Therapeutic applications of these medications range from treatment of both solid and leukemic malignancies to modulation of autoimmune conditions such as rheumatoid arthritis [6]. There are currently at least 15 clinically available TKIs on the market today. While these therapies are considered attractive options due to their perceived association with fewer side effects, it is now known that many of these therapies may have unintended consequences either as a result of their intended mechanism of action or off-target effects.

Serositis or serosal inflammation is a rare, but important side effect of the family of TKIs directed at the Bcr-Abl fusion product that has previously been reported in clinical trials. The incidence of effusions ranges from 7 to 35% in dasatinib, the agent most often associated with pleural effusions. Other agents such as imatinib, nilotinib, and bosutinib are associated with an incidence of serosities of less than 1% [7, 8].

The development of serosal inflammation in response to TKI agents can occur at any time, with previous studies reporting a range from 3 weeks to 2 years from the onset of therapy to the first documented episode of effusion [9]. The risk of serosal inflammation is thought to be dose dependent [5]. While the most common manifestation is a pleural effusion, concurrent pericardial effusions have been noted in up to 29% of cases [10]. Risk factors for the development of TKI-related serosal inflammation include a history of previous cardiac disease, hypertension, hyperlipidemia, autoimmune disease or a previous history of rash in response to TKI therapy [9]. In our case report, the presence of pericardial effusion notably occurred in the absence of a pleural effusion without a history of previous medical problems. To our knowledge, this is the first reported presentation of an isolated pericardial effusion after treatment with TKI.

Our patient presented with an exudative pericardial effusion with negative cultures and cytology, and withdrawal of the TKI resulted in improvement without recurrence after months of surveillance. In cases where fluid has been obtained, TKI-related effusions are reported to be exudative 80% of the time. In each of these cases, fluid cytology and bacterial/mycobacterial cultures yielded no evidence of malignancy or infection [10]. While general management of pericardial effusions is dependent on multiple parameters such as size of effusion, systemic symptoms (dyspnea, fever), and hemodynamic sequelae [11], identification of etiology and pericardiocentesis is imperative in patients with a history of malignancy to rule out both infection and recurrent malignancy. In cases where a negative workup is obtained, withdrawal of the TKI and/or changing to a different TKI within the same class prevents a recurrence of serosal inflammation [5], with steroid therapy providing more expeditious regression of inflammation within 3 days in highly symptomatic patients [10].

The mechanisms underlying the development of pleural and pericardial effusions have not been fully elucidated, but off-target tyrosine kinase inhibition and effect of TKIs on the function of the immune system have previously been implicated in their pathogenesis. Dasatinib, the Bcr-Abl target agent most often associated with effusions, is known to have multiple off-target effects including PDGFR-β, while imatinib, nilotinib, and bosutinib are all known to be weaker inhibitors of PDGFR-β [5]. Additional studies have also suggested that off-target effects of TKIs on the immune system may be responsible for the development of serosal inflammation [10]. This is supported by the association between serosal inflammation and the history of autoimmune disease, the exudative nature of effusions that are identified, and the historical response of highly symptomatic patients to steroids [10].

In conclusion, pericardial effusion is an important, possibly life-threatening complication that must be considered in any patient on TKI medication. Although less associated with newer TKI agents, we present the case of an isolated pericardial effusion that occurred after treatment with nilotinib. While thought to be dose dependent, pericardial effusion can occur at any time during therapy. After confirming the absence of malignant or infectious etiologies, withdrawal of the offending TKI is generally the standard treatment. With the increased use of TKIs for multiple applications, and with the increase in patients with a history of leukemia on long-term TKI therapy, it is incumbent upon providers to recognize this potentially life-threatening complication. Additionally, we report for the first time that TKI treatment can result in isolated pericardial effusion, in the absence of other effusions.

Disclosure Statement

The authors declare no conflict of interest and have no financial disclosures to report.

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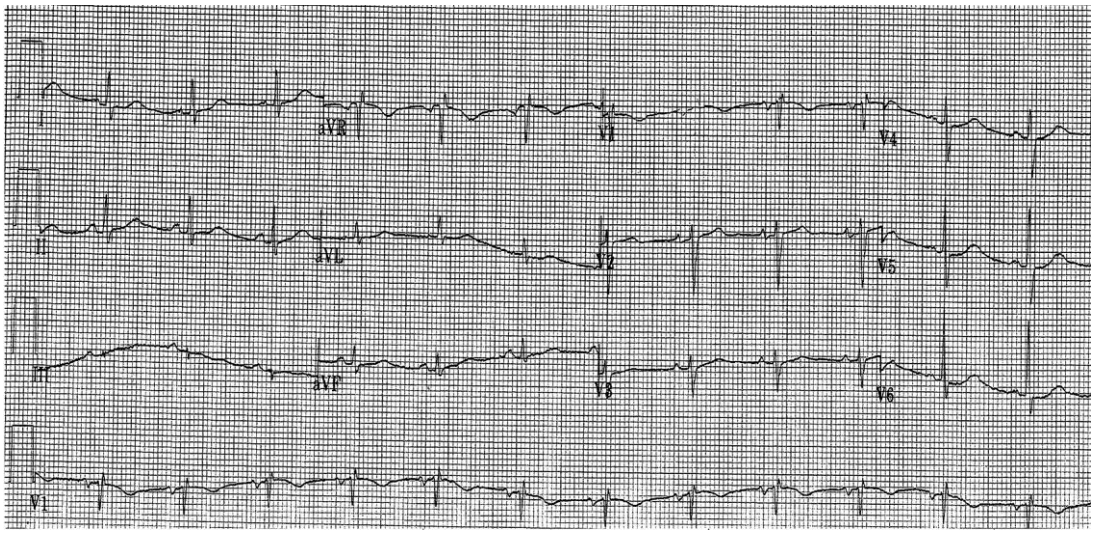

Fig. 1. Baseline EKG shows a normal sinus rhythm.

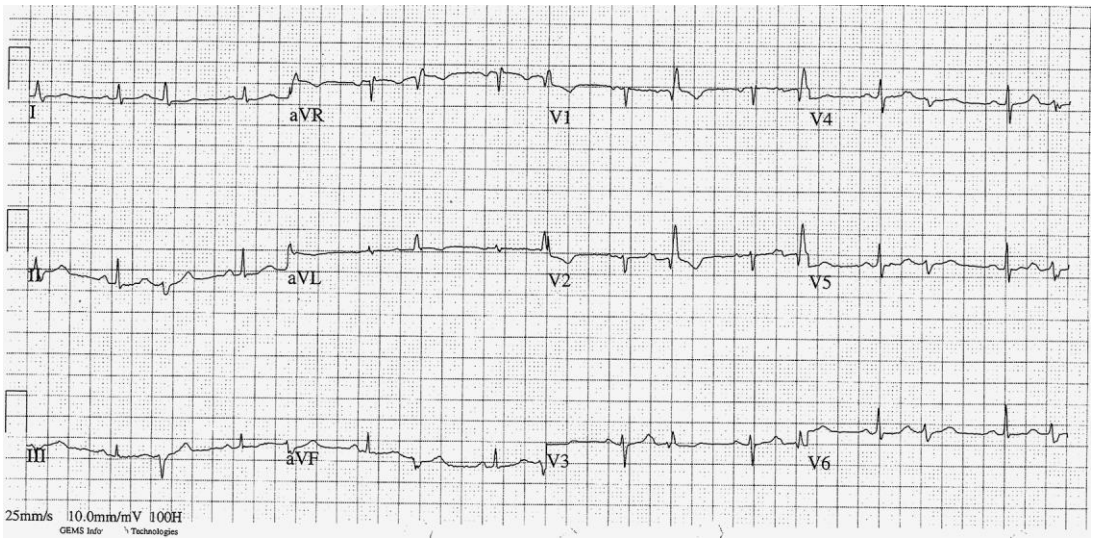

Fig. 2. Presenting EKG shows the evidence of low-voltage and electrical alternans.

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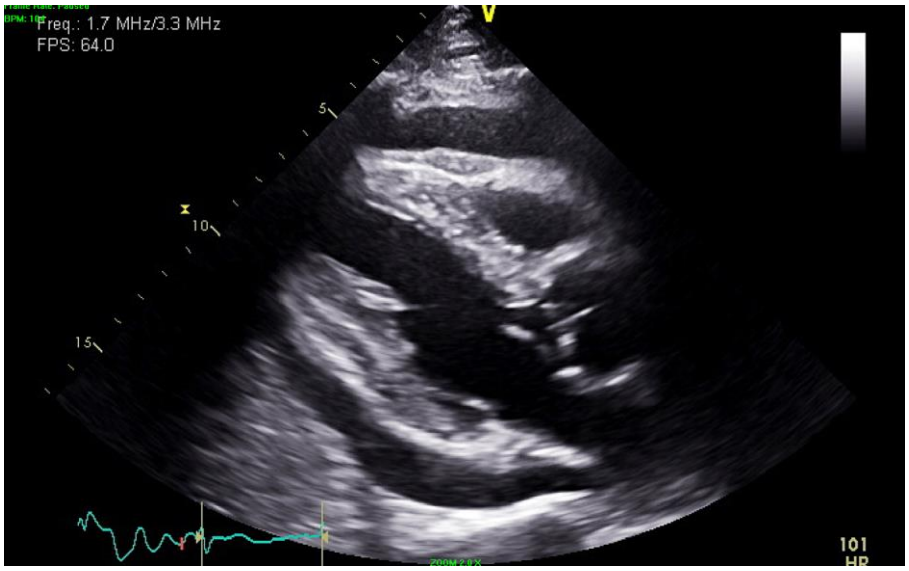

Fig. 3. Parasternal long-axis view of pericardial effusion on echocardiogram.

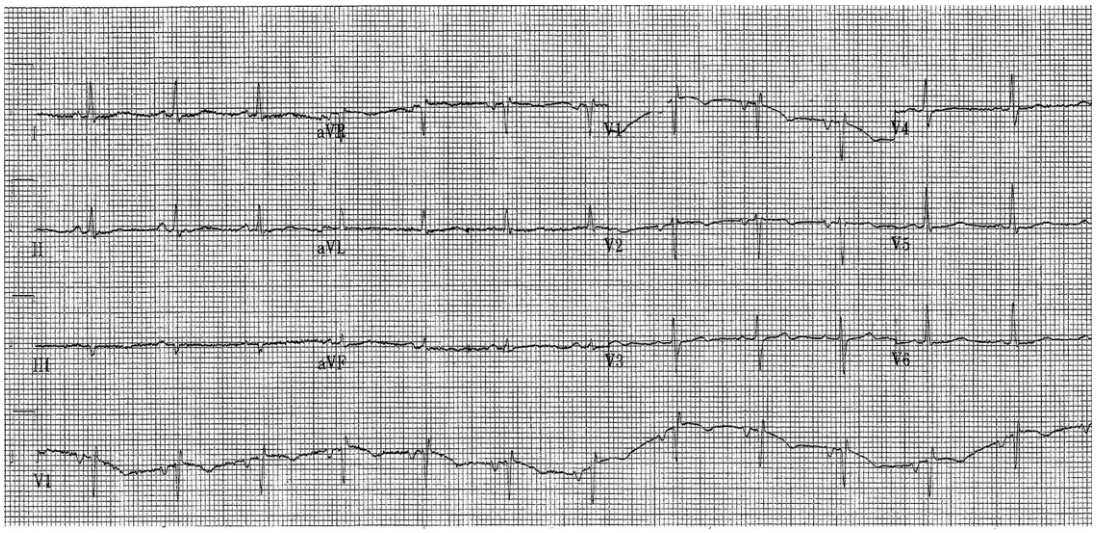

Fig. 4. Following pericardiocentesis, EKG shows a normal sinus rhythm.