Cardiac tamponade induced by dabrafenib and trametinib combination therapy for melanoma

Case report

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Abstract

Rationale: BRAF and MEK inhibitors (BRAF/MEK) are targeted therapy for proto-oncogene BRAF mutated metastatic unresectable melanoma. Compared to monotherapy, an increased cardiovascular toxicity is reported with the combination of Dabrafenib and Trametinib. This case report documents Grade 4 cardiac treatment emergent adverse effect of pericardial effusion and cardiac tamponade induced by this combination therapy.

Patient concerns: A 52 year old man presented with clinical stage II unresectable melanoma with BRAF V600E mutation, was initiated on treatment with Dabrafenib and Trametinib. He complained of generalised edema and increased his weight by 27 kg. This progressed to shortness of breath and he underwent echocardiogram which revealed cardiac tamponade.

Diagnoses: Emergent pericardiocentesis was performed. No defined pathology was demonstrated in laboratory analysis of pericardial fluid. Re-initiating treatment resulted in cardiac tamponade and pericardiocytomy was performed by video-assisted thoracic surgical (VATS). Pericardial biopsy revealed nonspecific chronic inflammation.

Interventions: Discontinuation of treatment with Dabrafenib and Trametinib and diuretics resolved peripheral edema. Cardiac function normalized after pericardiocentesis and pericardiocytomy.

Outcomes: Treatment with Dabrafenib and Trametinib caused significant peripheral edema and pericardial effusion resulting in cardiac tamponade. Naranjo score suggests probable association of treatment induced pericardial effusion and cardiac tamponade.

Lessons: This is the first documented report of pericardial effusion and cardiac tamponade induced by Dabrafenib and Trametinib. Cardiac toxicity of BRAF/MEK inhibitors is rare but clinicians must monitor for treatment emergent adverse effects.

Abbreviations: BRAF = proto-oncogene B-RAF, CT = computed tomography, ERK = extracellular signal-regulated kinase, MAPK = mitogen-activated protein kinase, MEK = mitogen-activated protein kinase, PD-1 inhibitors = programmed death 1 inhibitors, PET = positron-emission tomography, VATS = video-assisted thoracoscopic surgery.

Keywords: BRAF and MEK inhibitors, cardiac toxicity, dabrafenib, malignant melanoma, pericardial effusion and cardiac tamponade, targeted therapy, trametinib combination therapy

1. Introduction

Recognition of the proto-oncogene B-RAF (BRAF) mutation in melanoma has provided us with targeted therapy. The use of BRAF and MEK inhibitors has been approved as monotherapy and in combination.[1] It was seen in the BREAK clinical trials, that dabrafenib as a single agent did not demonstrate significant cardiovascular toxicity.[2] Trametinib is reported to cause hypertension, peripheral edema, and cardiomyopathy, which is attributed to the inhibition of the cardioprotective function of the MAPK pathway.[3] Combination therapy increased the cardiovascular toxicity, causing decreased ejection fraction, pulmonary embolism, cardiomyopathy, hypertension, and hypotension.[1,4] It is postulated that the disruption of the MEK-ERK axis explains the pathophysiology of cardiovascular toxicity.[3]

This case report is the first to document pericardial effusion resulting in cardiac tamponade due to the combination treatment of dabrafenib and trametinib.

The patient's anonymity and consent were guaranteed, in agreement with the Declaration of Helsinki.

2. Case presentation

A 52-year-old male presented in 2015 with malignant melanoma of the left groin requiring wide local excision, superficial, and deep groin dissection. Lymph nodes were positive for residual malignant melanoma. Imaging with computed tomography (CT) and positron-emission tomography (PET) scans documented clinical stage III unresectable melanoma and molecular pathology was positive for BRAFV600E mutation. Biochemical parameters including lactate dehydrogenase were within normal limits. He had no comorbidities or underlying autoimmune disorders.
Treatment with ipilimumab (cytotoxic T-lymphocyte-associated protein-4 inhibitor) was initiated.

At the time of initiating ipilimumab (3 mg/kg q 3 weeks), there was evidence of edema to the left lower limb. Doppler imaging confirmed an occlusive thrombus of the left lesser saphenous vein for which he was put on low-molecular weight heparin. He completed 4 cycles of ipilimumab between March 30 and June 4, 2015. His only complaint was an intermittent mild erythematous maculopapular rash. Repeat PET scan on July 6, 2015 showed progression of disease. Treatment was switched to dabrafenib and trametinib combination initiated on August 10, 2015, but discontinued after 2 weeks because of dramatic weight gain of 27 kg over a 6-week period.

Along with gross peripheral edema, he developed pericardial effusion confirmed by echocardiography on August 31, 2015 which did not improve with medical management or withholding dabrafenib and trametinib. Repeat echocardiography revealed increasing pericardial effusion and he was admitted on September 25, 2015 with cardiac tamponade requiring pericardiocentesis draining 750 mL of pericardial exudate fluid. Cytopathology was negative for malignancy and cultures were sterile. Work up for autoimmune etiology was negative. He was treated with steroids and diuretics, with good response.

Possibility of late onset autoimmune pericarditis and cardiac tamponade was considered and attributed to the immune related adverse event of ipilimumab which resolved promptly with the use of corticosteroids. Manufacturers of dabrafenib and trametinib were contacted to confirm no previous reports of pericardial effusion with the combination therapy.

Treatment with dabrafenib and trametinib was restarted in November 20, 2015 after cardiac assessment was reported as normal. However, on December 27, 2015 due to reaccumulation of pericardial effusion treatment was interrupted. Pericardial window was required and biopsy reported as nonspecific chronic inflammation. The pericardial fluid analysis revealed a sterile exudate with no evidence of malignancy. Unfortunately during this hospitalization, there was closure of pericardial window requiring VATS for a repeat pericardiectomy which drained 1.5 L of fluid. He developed idioventricular arrhythmia which responded to treatment with amiodarone. Subsequent echocardiogram revealed ejection fraction of 61%. His renal function remained normal with creatinine of 109 μmol/L due to diuretics which he was receiving continuously.

Once again a trial with combination therapy of dabrafenib and trametinib was undertaken from January 15, 2016 but discontinued after 2 weeks due to rapid accumulation of pericardial fluid and peripheral edema. Subsequently, he received 4 cycles of ipilimumab at 1 mg/kg from January 2016 and is still receiving pembrolizumab at 2 mg/kg every 3 weeks from May 2016. CT scan done on April 2018 did show progression of disease with new 5 mm pulmonary nodule in right upper lobe.

3. Discussion

Treatment options for metastatic melanoma have evolved over the past decade. The presence of BRAF mutation provides the option for treatment with BRAF inhibitors such as vemurafenib and dabrafenib. Resistance to the treatment develops by reactivation of the mitogen-activated protein kinase (MAPK) pathway, combination therapy with MEK inhibitors, such as trametinib, improves the overall survival. Knowledge of the MAPK signaling pathway for therapeutic targets suggests pathophysiologic explanations for the cardiovascular toxicity linked to these treatments. The effects of dual inhibition on MEK-ERK activity upregulate cluster differentiation 47 (CD47), a transmembrane protein causing reduction in nitric oxide bioavailability. Nitric oxide and prostacyclin are thought to have vascular protective effects.[13]

Serious adverse reactions with MEK and BRAF inhibitors are uncommon and usually occur in the initial days, or after months of treatment. In the phase III COMBI-d trial, treatment related cardiac adverse events were reported as a decrease in left ventricular ejection fraction in 5% of patients.[14] Significant peripheral edema (seen more commonly with MEKs) was reported in 31% but these were not documented with simultaneous echocardiograms to assess the effect on cardiac function.[6]

The BRAF inhibitors are reported to cause hypertension, and QT interval prolongation as seen on ECG.[15] Unlike Dabrafenib we have reports of vemurafenib induced pericarditis associated with effusions and cardiac tamponade.[7] Mahoney et al demonstrated that appropriate treatment of cardiac tamponade and vemurafenib discontinuation, resulted in complete resolution with the ability to resume treatment.[8]

Cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction) occurred in 7% of patients treated with trametinib in the phase I study.[16] The selective MEK inhibitors have shown varying grades of cardiac dysfunction in the phase II trials of Binimetinib and Selumetinib.[9,10] The median time to onset of cardiomyopathy was 63 days (range: 16–156 days).

In this case, we did consider late onset of pericardial effusions due to ipilimumab, at the initial presentation. This has been seen in patients receiving ipilimumab.[11] A similar report of late onset pericardial tamponade 24 weeks after completing ipilimumab was associated with bilateral pleural effusions and recurrent immune monoarthritis suggestive of autoimmune phenomena.[12]

The clinical trials have demonstrated 10% to 40% of patients treated with ipilimumab have grades 3 to 4 immune-related adverse events such as enterocolitis, hepatitis, dermatitis, and endocrinopathy.[13] Less than 1% have pericarditis, nephritis, pneumonitis, meningitis, uveitis, or hemolytic anemia.[14] Immune responses often evolve over months and can explain the delayed timing of adverse events.[15] In our patient, there were no adverse events after restarting ipilimumab which can confidently exclude it as the culprit.

Increased use of Dabrafenib and Trametinib will reveal more cardiovascular complications which could be attributed to the “two hit hypothesis.”[13] The cardiac toxicity is sum of two events like hypertension, cardiac ischemia or exposure to toxic drugs resulting in clinically apparent cardiac injury caused by the BRAF/MEK inhibitors.[4]

The complexity in treating patients with targeted therapy for malignant melanoma may result in overlap toxicities. Many of the side-effects of MEK and BRAF inhibitors are similar to immune check point inhibitors and anti PD-1 inhibitors. We attribute this patient’s peripheral edema and pericardial effusions to the combination of trametinib and dabrafenib since rechallenging resulted in the immediate recurrence of pericardial effusion and cardiac tamponade.

We switched our patient to ipilimumab at 1 mg/kg for 4 cycles and pembrolizumab 2 mg/kg in accordance to the keynote 029 trial (clinical trial information: NCT02089685). He continues to have mild adverse events such as grade 1 erythematous rash, but no decrease in left ventricle ejection fraction or recurrence of pericardial effusion. It is reassuring to know that the discontinuation of dabrafenib and trametinib resulted in complete normalization of cardiac function.
4. Conclusion
To our knowledge, this is the first reported case of pericardial effusion and cardiac tamponade due to combination treatment with dabrafenib and trametinib. This grade 4 treatment emergent adverse effect of BRAF/MEK inhibitors highlights the necessity of cardiovascular monitoring during therapy.

Author contributions
VRS and TA contributed equally to the drafting of the study and approved the final version.

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