CASE REPORT

Post-transfusion breathlessness in a patient with acute myeloid leukaemia

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SUMMARY

We present a case of a 38-year-old man with acute myeloid leukaemia (AML) in remission who developed sudden-onset chest pain and shortness of breath 30 min after receiving a blood transfusion. His condition deteriorated and required transferring him to the intensive care unit. The initial differential diagnosis was wide given his immunosuppression, recent chemotherapy, hospitalised status and receipt of blood products. Extensive work up concluded Coxsackie virus-induced myopericarditis as the cause of his symptoms. He was treated with colchicine monotherapy for 3 months and remained without recurrence of pericarditis at 3 months of follow-up.

BACKGROUND

The differential diagnosis for acute onset chest pain and shortness of breath is very broad, and the most clinically important considerations include acute cardiopulmonary events.

In patients who are receiving a blood transfusion at the time of symptom onset, a transfusion reaction is an important differential. Both transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) can give these symptoms, alongside haemolytic and non-haemolytic reactions. In a patient with appropriate risk factors, myocardial infarction and pulmonary embolism remain important considerations. Although many other diagnoses can give similar symptoms, acute myopericarditis is an important differential. Viral infections remain the most common cause of myopericarditis although alternate causes such as drug reactions, infections, malignancy, connective tissue disease, cardiac injury and myocardial infarction exist.

Oncology patients who develop myopericarditis may have particular risk factors for specific aetiological agents. Multiple chemotherapeutic agents (especially anthracyclines) have been associated with myopericarditis, and direct tumour infiltration and paraneoplastic syndromes may also contribute. They may also be at risk of atypical infections due to their immunocompromised status.

Determining the cause is especially important in oncology patients, as unique considerations must be taken into account while treating these patients. We present a patient with acute respiratory decompensation after a blood transfusion, who was found to have Coxsackie virus-induced myopericarditis.

CASE PRESENTATION

A 38-year-old man with acute myeloid leukaemia (AML) in remission following induction

chemotherapy with cytarabine and daunorubicin (7 +3 regimen) and three cycles of high-dose cytarabine consolidation (last, 1 week ago), presented to the emergency department with fever. The patient had had one admission each for neutropaenic fever following each of his prior cytarabine cycles, with resolution of fever with supportive care and empiric antimicrobial therapy with no clear source identified. He endorsed a history of shortness of breath on exertion. Other review of symptoms was negative for any infectious foci.

Medications included prophylactic ciprofloxacin, fluconazole and acyclovir, with which he reported compliance. He had last taken a filgrastim (granulocyte colony-stimulating factor, G-CSF) injection 2 days prior.

He was febrile to 40° Celsius (104° F) and tachycardic. Systemic examination revealed conjunctival pallor and diffuse petechiae on lower extremities. A peripherally inserted central catheter (PICC) line in the right arm was observed with no surrounding erythema, swelling, tenderness or discharge. The rest of the examination was unrevealing.

Initial laboratory evaluation revealed haemoglobin 6.1 gm/dL, white cell count $80 \times 10^9/L$ and platelet count $<5 \times 10^9/L$. Basic metabolic profile was unremarkable. Troponin T levels were <0.01 ng/mL (repeated thrice) and an ECG revealed sinus tachycardia. Chest X-ray showed clear lung fields without cardiomegaly with PICC line tip in the distal superior vena cava. No signs of haemolysis or disseminated intravascular coagulation were noted and peripheral blood smear demonstrated pancytopenia with no abnormal cells. Blood and urine cultures were drawn, and empiric antimicrobial therapy with vancomycin and piperacillin-tazobactam was initiated. The patient was transfused with two units of platelets and a unit of packed red blood cells (PRBC) in the first 24 h with an appropriate rise in blood indices. His fever subsided over 48 h with no clear source of infection identified and cultures reporting no growth. Antibiotics were discontinued after 48 h and a plan for discharge was made. His haemoglobin level, which had risen to 7.2 g/dL after the first PRBC transfusion, had fallen to 6.8 g/dL at this time. A decision to transfuse another unit before discharge was made. His shortness of breath on admission improved with the blood transfusion, and was attributed to anaemia.

Thirty minutes after receiving a unit of matched PRBCs, the patient reported of midsternal pressure and acute onset of shortness of breath. He also reported of nausea but did not have emesis. He

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denied any paralumbar pain. His oxygen saturation fell to 80% on room air and rose to 93% on 50% venturi mask. He was haemodynamically stable with normal vital signs, temperature 37.8° Celsius, regular pulse rate of 126/minute, blood pressure 147/87 mm Hg and respiratory rate 28/minute. The patient was noted to be diaphoretic and unable to complete sentences due to shortness of breath. Jugular venous pressure was elevated to the mid-neck and thoracic auscultation revealed new bibasilar lung crackles without murmurs, rubs, or gallops. The remainder of his examination was unremarkable. No pulsus paradoxus or Kussmaul sign was noted. He had continued urine output.

INVESTIGATIONS

Initial laboratory tests showed absence of haemolysis. Urine analysis revealed straw-coloured urine without new casts. The blood bank rechecked the blood and concluded that no donor-recipient mismatch had occurred. A D-dimer level returned at 0.38 mg/L. Chest X-ray (CXR) demonstrated new onset hazy opacities in bilateral lung bases and vascular redistribution consistent with pulmonary oedema. An EKG (sinus tachycardia at admission) was notable for diffuse ST elevation. Serial troponin T (<0.01 ng/mL at admission) levels were uptrending (0.54, 1.21 and 1.24 ng/mL at 0 h, 3 h and 8 h). Serial CK-MB levels mirrored the troponin T rise (22, 42, 67 ng/mL). NT-proBNP level was 703 pg/mL (no baseline, normal <300).

A bedside ultrasound did not reveal a cardiac tamponade. Emergent transthoracic echocardiogram showed a dilated left atrium with minimal pericardial effusion with no major valvular or wall motion abnormalities. A cardiac MRI demonstrated sub-epicardial and pericardial delayed enhancement consistent with myopericarditis. The left atrium was dilated and there was mild pulmonic regurgitation. Other elements of the cardiac MRI were normal.

Multiple viral studies, including HHV-6 PCR and parvovirus PCR, respiratory viral DFA (influenza A, influenza B, parainfluenzae 1–3, respiratory syncytial virus A and B, human rhinovirus, human metapneumovirus, adenovirus B/E and C) and influenza antigen tests were negative. The result of the Coxsackie B virus IgM antibody type 4, reported after discharge, returned positive at 1:80 dilution. Coxsackie virus PCR was not performed.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this patient's acute decompensation in the setting of recent blood transfusion included several well known complications of transfusion.

Acute haemolysis was excluded given the negative haemolysis laboratory results, stable creatinine, clean urinalysis and continuing urine output. Acute hypoxic respiratory failure was very suspicious for TRALI and CXR haziness supported this diagnosis, although the classic acute respiratory distress syndrome did not manifest. The patient was treated for respiratory failure empirically with oxygen and the blood bank was suitably informed. TACO was also a diagnostic consideration given the clinical and laboratory signs of volume overload (bibasilar crackles, elevated JVP, CXR, elevated NT-proBNP) and recent blood transfusion. The patient had received multiple transfusions in the past and an allergic/anaphylactic event was considered; however, he did not have stridor, wheezing or rashes on examination.

Given the patient's non-significant cardiac history and young age, an acute coronary syndrome (ACS) was considered unlikely and the ECG changes went against ACS despite troponinemia. A pulmonary embolism was excluded with a normal D-dimer level. Transthoracic echocardiogram excluded acute cardiac

valvular disease and the patient was normotensive, excluding hypertension-induced flash pulmonary oedema as a diagnosis.

However, the one diagnosis that explained all the physical, laboratory, imaging and EKG findings was myopericarditis. EKG changes were classic for pericarditis and cardiac myocyte enzyme leakage supported a component of myocardial damage. It is possible that the increased circulatory volume after the transfusion tipped our patient into heart failure. Enlarged left atrium indicated volume overload and cardiac MRI confirmed myopericarditis as the diagnosis. The patient's profound respiratory distress and increasing oxygen requirements were likely due to superimposed volume overload from transfusions.

The aetiology of myopericarditis, however, was not immediately clear. The patient had received anthracycline-based chemotherapy a few months prior. The cardiotoxicity of anthracyclines is well known, although no specific diagnostic tests exist. Although dose-dependent reduction in ejection fraction is most common, rare cases of delayed myopericarditis have also been reported. Our patient had only received one other chemotherapy drug, cytarabine. Cytarabine is mostly associated with cerebellar and corneal toxicity although rare reports have outlined cytarabine-induced pericarditis. Our patient had recently received high-dose cytarabine and this remained an important differential. Our patient was febrile on presentation although without focal signs. An infection could also cause this and a positive Coxsackie viral titre pointed to viral infection as the inciting event.

TREATMENT

The patient's chest pain did not improve with sublingual nitroglycerin, although venturi mask placement improved the oxygen saturation and the patient was transferred to the medical intensive care unit. Small doses of intravenous morphine improved the chest pain and shortness of breath. The patient was not anticoagulated given the low suspicion for ACS and thrombocytopenia. He received one dose of intravenous furosemide and a nitroglycerin drip was initiated to control flash pulmonary oedema and reduce cardiac preload. A water and salt restricted diet was initiated.

After stabilisation (he did not require intubation and had minimal oxygen requirements after 6 h and was tolerating room air 12 h later), a decision regarding the best agent and the duration of therapy to treat his pericarditis was made.

Possible agents included non steroidal anti-inflammatory drugs (NSAIDs), steroids and colchicine, alone and in combination. Given our patient's extensive chronic thrombocytopenia and risk for bleeding, NSAIDs were not considered. Our patient had frequent admissions for neutropenic fever and was at high risk for infection and thus steroids were out of favour. Colchicine emerged as the 'safest' of the three agents and, given recent promising studies, was chosen as the drug of choice in our patient. Colchicine therapy (0.6 mg twice a day orally) was initiated. He was discharged after a filgrastim injection, on prophylactic acyclovir and fluconazole and colchicine.

OUTCOME AND FOLLOW-UP

Our patient had no recurrence of pericarditis and did not have any notable gastrointestinal side effects from colchicine. Three months after discharge, however, the patient presented again with neutropenic fever. He was not receiving any chemotherapy at this time. Persistent pancytopenia (initially concerning for colchicine toxicity) prompted a bone marrow biopsy, which revealed 20% blasts, that is, recurrent AML. Salvage chemotherapy with FLAG-IDA (fludarabine, cytarabine, G-CSF and

idarubicin) was initiated. Unfortunately, after just one cycle, the patient developed shortness of breath and respiratory failure with chest CT demonstrating a mass in the left upper lung lobe. A bronchoalveolar lavage (BAL) was performed with suctioning of turbid fluid, which contained 70 nucleated cells/ μL (differential 2% neutrophils, 47% lymphocytes, 47% monocytes and 4% other cells). Cultures only grew respiratory flora and blood cultures remained negative. Acid-fast bacilli and sputum smear was unrevealing. Given the clinical picture, a fungal aetiology was considered although fungal blood cultures, BAL cultures and serum complement fixation remained negative. Despite supportive care and broad spectrum antibiotics and antifungal agents, our patient had worsening clinical status and care was ultimately withdrawn.

DISCUSSION

Acute pericarditis is present in 0.2% of patients hospitalised for cardiovascular reasons, and accounts for 5% of emergency department admits related to non-ischaemic chest pain.^{1 2} In most cases, extensive work up for aetiology is not completed because the course of the disease is mild and self-limited. Idiopathic pericarditis, accounting for about 85% of diagnosed cases of pericarditis, is thought to be largely accounted for by viral infections. Infection with parvovirus B₁₉, human herpes virus 6 (HHV-6) or Coxsackie virus, is thought to be the most common. Our patient was found to have a positive titre for Coxsackie virus B, which is transmitted via the faecal-oral route. It usually only causes symptoms of mild gastrointestinal distress and can also resemble the common cold. However, pericarditis, myocarditis and aseptic meningitis are possible. Our case, therefore, emphasises the importance of keeping the most common cause at the top of the differential. In studies, neoplasia, tuberculosis, autoimmune disorders and bacterial infections have been shown to be other important causes, with specific treatments.²⁻⁵ Drug-related pericarditis is also an important aetiology. Identifying a drug as the cause is important, because stopping the offending drug reduces recurrence. Several chemotherapeutic agents such as anthracyclines and 5-fluorouracil are commonly associated with cardiotoxicity. Important in this patient, however, are several prior reports of pericarditis after treatment with cytarabine. In these patients, the mechanism is thought to be a hypersensitivity reaction in response to cytarabine.^{6 7} We included cytarabine-induced pericarditis in our differential, which would have had ramifications for our patient's chemotherapeutic regimen.

The standard of care for patients with pericarditis is directed towards the presumed diagnosis of viral pericarditis. NSAIDs and colchicine are first line and have been shown to reduce recurrence more than NSAIDs alone.⁸ If there is an identifiable and treatable aetiology, then specific treatment is also started. This can include antibiotics in bacterial infections or immunosuppressive agents in connective tissue disease.

In our patient, we were hesitant to use NSAIDs, given the concern for current and persistent thrombocytopenia. Steroids were not given owing to their immunosuppressive properties. Colchicine as monotherapy has been shown to be effective in reducing the recurrence of pericarditis, so it is a reasonable

choice as a monotherapeutic agent.⁹ Our patient did not have a recurrence within the 3 months of follow-up until his death.

Patients with AML have unique risk factors including receipt of chemotherapy and blood products. One must consider these factors before making any diagnosis. Our case highlights the importance of considering drug-induced pericarditis while realising that viral infection still remains the most important aetiology. It also emphasises the value of colchicine as monotherapy for chemotherapeutic patients who may have thrombocytopenia.

Learning points

- ▶ Patients with acute myeloid leukaemia have unique risk factors; transfusion reactions and chemotherapy-induced adverse effects should always be considered in patients with an appropriate history, but may not always be the cause of the patient's symptoms.
- ▶ Troponinemia and EKG changes do not always equate to an acute coronary syndrome event, and should be interpreted in the right clinical setting.
- ▶ Viral infections remain the most common cause of myopericarditis and no specific antiviral therapy is usually available.
- ▶ Colchicine can be used as monotherapy for myopericarditis in patients with contraindications to non-steroidal anti-inflammatory drug and steroid use.

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