Netherlands
The Journal of Medicine

SPECIAL REPORT

Chest pain in sickle cell disease

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ABSTRACT

The differential diagnosis of chest pain in a patient with sickle cell disease is difficult and may encompass several serious conditions, including chest syndrome, pulmonary embolism and infectious complications. In this manuscript we provide an overview on the various underlying diseases that may cause chest pain in patients with sickle cell disease and provide clues for a proper diagnostic workup.

KEYWORDS

Acute chest pain, myocardial infarction, sickle cell disease, vaso-occlusive crisis.

INTRODUCTION

A clinical pathology conference is held each trimester at the Department of Internal Medicine of the Academic Medical Centre Amsterdam. A few weeks before the conference, a senior resident is presented with a 'paper' case to be solved. The resident is provided with some but not all details on the case, such as clinical, laboratory and radiological data (no reports). Based on this information, the resident puts together a case with a focus on clinical reasoning leading to a provisional diagnosis. Afterwards, the clinician who provided the case reveals the actual diagnosis and clinical course. Here, a recent case is reported of a young woman with sickle cell anaemia who presented with acute chest pain.

THE CASE

A 35-year-old woman presented at the emergency room with chest pain. She was known with sickle cell anaemia combined with heterozygous alpha-thalassemia (-α/αα) with frequent painful crises. The sickle cell anaemia was complicated by symptomatic cholecystolithiasis and avascular necrosis of the femoral heads, for which cholecystectomy and bilateral total hip replacement had been performed. Two years before presentation she had had an ischaemic stroke from which she had residual impairment. Due to multiple blood transfusions she had developed iron overload for which she was treated with the iron chelator deferiprone. Because of chronic pain she frequently used cannabis, methadone, NSAIDs and paracetamol. As a consequence, managing her painful crises had become increasingly difficult. A port-a-cath had been placed to secure venous access. Recently vitamin D deficiency with severe hypocalcaemia was diagnosed, for which she was prescribed colecalciferol and calcium carbonate.

At presentation she complained of chest pain located around the sternum and the port-a-cath since a few days. The pain worsened upon movement; otherwise no provoking factors could be discerned. The patient had not been ill, nor had she had any fever. She was not dyspnoeic and she had no cough. She had suffered palpitations. In addition, she had experienced painful muscle cramps. On physical examination the patient appeared in pain but not ill. Her blood pressure was 145/55 mmHg and her pulse 90 beats/minute and regular; the temperature was normal. Palpation of the skin overlying the port-a-cath was painful, but there was no redness or swelling. Otherwise the physical examination was unremarkable.

CLINICAL REASONING

This case concerns a young woman with severe and complicated sickle cell anaemia presenting with (semi) acute chest pain, palpitations and muscle cramping.

Sickle cell disease (SCD) is characterised by recurrent painful vaso-occlusive crises and progressive organ damage leading to premature death.

A single mutation in the β-globin gene results in the formation of haemoglobin S (HbS). SCD is caused by homozygosity for this mutation (sickle cell anaemia; HbSS), or by heterozygosity for the HbS gene in combination with other haemoglobinopathies such as HbSC or HbS-β-thalassaemia. Upon deoxygenation, a hydrophobic motif in the HbS tetramer causes the HbS molecules to polymerise resulting in sickling of the erythrocytes.[1] Sickled erythrocytes interact with neutrophils and endothelium which leads to vaso-occlusion resulting in ischaemia and haemolysis and subsequently activation of inflammation and coagulation. Next, reperfusion of ischaemic tissues causes oxidative stress (reviewed by Nur, *et al.*[2]). In addition to the acute ischaemic injury to affected organs by vaso-occlusion, these processes lead to vasculopathy and chronic organ dysfunction such as cerebrovascular disease, renal failure and pulmonary hypertension.[3]
Alpha thalassaemia results from impaired production of one to three of four alpha globin chains. Alpha thalassaemia minima (-α/αα) is generally asymptomatic, but in patients with SCD, concurrent alpha thalassaemia increases the frequency of vaso-occlusive crises, acute chest syndrome and osteonecrosis.[4,5]

This patient presents with three symptoms which may or may not be related: (semi) acute chest pain, palpitations and muscle cramping. As (semi) acute chest pain may indicate serious pathology, this symptom should be explored with priority.

Painful vaso-occlusive crisis
Periodic episodes of excruciating musculoskeletal pain are the hallmark of SCD. Although the majority of crises arise spontaneously, they can be provoked by external factors such as infections, stress, dehydration or extreme physical exertion. The main determinants for the frequency of crises are the haematocrit and percentage HbF.[6] Recurrent vaso-occlusive crises give rise to progressive organ damage such as avascular necrosis of the femoral heads, renal failure, neurological impairment and functional asplenia.
Painful crises are the most common reason for admission and a major cause of morbidity and reduced quality of life.[7] In adult patients, frequent pain is even associated with a higher mortality rate. The variability of episodes requiring clinical care is high; up to 40% of patients have less than one crisis per year, whereas 1% of patients have more than six episodes.[6] Of note, a recent prospective cohort study using daily self-assessment diaries revealed that pain is even more prevalent; pain was reported in 55% of analysed patient days, while 29% of patients reported pain almost daily. In addition, the majority of crises were managed at home.[8] The discrepancy between the actual prevalence of pain and incidence data derived from studies defining painful crisis by the need for utilisation of health care may lead to miscommunication and undertreatment. For example, a survey among haematologists and emergency department physicians regarding their perceptions concerning sickle cell pain revealed that a considerable portion of them believed that >20% of their patients are addicted to opioids.[9]
This patient is known with chronic pain, analgesia use and frequent crises; however, she did not report to have a crisis at presentation. Therefore a vaso-occlusive crisis as the cause of the present chest pain is less likely.

Acute chest syndrome
Acute chest syndrome is the second most common cause of hospitalisation in SCD. It is a serious clinical condition and a major cause of death in SCD. The aetiology is multifactorial; the syndrome is set off by pulmonary infection or infarction by bone marrow-derived fat emboli. Atelectasis resulting from hypoventilation due to musculoskeletal pain and increased airway reactivity may further add to the pathophysiology. Local shunting leads to deoxygenation and sickling of erythrocytes and vaso-occlusion (reviewed by Gladwin, *et al.*[10]). Clinically, the acute chest syndrome is defined by the presence of a new pulmonary infiltrate involving at least one lung segment in combination with fever (80%) and pulmonary symptoms such as coughing (62%), dyspnoea and/or chest pain (40%). Typically, the acute chest syndrome presents three days after the start of a vaso-occlusive crisis. Rapid diagnosis and treatment are warranted; around 13% of patients require ventilation during the course of the disease and mortality is 3%.[10] Although the index of suspicion for this syndrome should always be high, this diagnosis seems less likely based on the absence of pulmonary symptoms and fever in this patient.

Causes indirectly related to SCD
The life expectancy of patients with sickle cell anaemia is greatly diminished at approximately 40 years.[11-13] Death is frequently sudden and unexpected (40.8%) and commonly occurs within 24 hours after presentation to the hospital.[14] Cardiopulmonary causes account for a significant proportion of deaths. In one single-centre cohort study in 240 patients with SCD, 43 patients died during a five-year observation period (median age 39 years). Of these, 11 died of cardiac causes (pulseless arrest (n=5), congestive heart failure (n=3), myocardial infarction (n=3)) and six of pulmonary causes (including four patients with fatal pulmonary embolism).[13] Therefore, causes of chest pain unrelated to SCD should be seriously considerated.

Pulmonary embolism
SCD is characterised by chronic activation of coagulation; nearly all components of haemostasis are altered

(reviewed by Ataga, *et al.*[15]). The actual risk of venous thromboembolism (VTE) attributable to SCD is not well known, largely because of difficulties in distinguishing it from fat emboli or thrombosis in situ, but also because of the high prevalence of (SCD-related) comorbidities in patients with SCD. Furthermore, almost all markers of coagulation including D-dimers are disturbed in SCD,[16] which hampers the diagnostic process. However, studies indicate that SCD is probably an independent risk factor for VTE. A retrospective analysis of the National Hospital Discharge Survey (US) revealed that 0.44% (7000 of 1,581,000) of patients with SCD had a discharge diagnosis of PE compared with 0.12% (59,000 of 48,611,000) of African Americans without SCD. The incidence of deep vein thrombosis did not differ, indicating that at least some of the cases of PE may have been in situ thrombi.[17] In a recent case-control study the attributable risk of sickle cell trait (SCT) for VTE was calculated to be 7%; the odds ratio (OR) for VTE was 1.8 (95% CI, 1.2-2.9) in subjects with SCT versus subjects homozygous for the wild-type allele. The OR for pulmonary embolism and sickle cell trait was even higher at 3.9 (CI 2.2-6.9).[18]
Although our patient does not have 'typical symptoms' of pulmonary embolism, this diagnosis should not be rejected before a satisfactory alternative diagnosis is made.

Cardiac causes
Cardiac complications are a leading cause of morbidity and mortality in adult patients with SCD. Cardiac abnormalities can be divided into three major groups. First, cardiac output is increased due to chronic anaemia and recurrent episodes of hypoxia. In addition, pulmonary hypertension is found in up to 6% of patients with SCD (with chronic haemolytic anaemia as central risk factor).[19] Together, this may result in progressive diastolic and systolic dysfunction and eventually in overt left- as well as right-sided chronic heart failure (reviewed by Voskaridou, *et al.*[20]). Secondly, patients with SCD are prone to arrhythmias; a prolonged QTc time is found in up to 40% of patients in steady state.[21] The use of medication such as methadone contributes to QTc prolongation. Furthermore, continuous monitoring of 30 patients during the first 24 hours of a vaso-occlusive crisis revealed arrhythmias in 24 patients, of both atrial (60%) and ventricular (67%) origin. Nine of these patients even had 'complex arrhythmias' including two with episodes of ventricular tachycardia.[22] Thirdly, patients with SCD have an increased risk of ischaemic heart disease. Acute myocardial infarction is a common cause of sudden death in SCD.[13,23] However, cardiac ischaemia is often insufficiently recognised as a typical vaso-occlusive crisis presents with diffuse musculoskeletal pain or atypical chest pain and patients are young. Therefore, the true incidence of cardiac ischaemia is not well known.

Our patient has new palpitations and atypical chest pain. Considering the possible sequelae, cardiac pathology should be excluded.

Other causes
As we have only sparse knowledge about the symptoms and signs in this patient, at this point many alternative explanations for the chest pain (including malfunction or infection of the port-a-cath, pleuritic, pericardial, myogenic, osteogenic (osteomalacia), costochondral and gastrointestinal causes) cannot be definitely ruled out.

CLINICAL DIAGNOSIS

Based on the sparse clinical information provided, the most obvious causes of chest pain in a patient with SCD, namely vaso-occlusive crisis and acute chest syndrome, seem less likely.
Considering the high incidence of life-threatening cardiac and thromboembolic events in patients with SCD, first of all myocardial ischaemia should be ruled out and next pulmonary embolism.

ADDITIONAL TESTING

Guided by the differential diagnosis, additional laboratory testing and an electrocardiogram were performed (*table 1* and *figure 1*). Laboratory results showed anaemia with

Table 1. *Laboratory results*

Variable	Reference range		
Haematology			
Haemoglobin (mmol/l)	7.4-9.9	5.2	↓
Leucocyte count (x 10^9/l)	4.5-11.0	17.2	↑
Platelet count (x 10^9/l)	150-400	334	
Chemistry			
Calcium (mmol/l)	2.20-2.60	1.42	↓
Phosphate (mmol/l)	0.70-1.50	0.77	
Creatinine (µmol/l)	50-90	52	
Albumin (g/l)	35-50	44	
Alkaline phosphatase (U/l)	40-120	158	↑
γ-Glutamyltransferase (U/l)	5-40	22	
ASAT (U/l)	10-30	36	↑
ALAT (U/l)	5-35	25	
Lactate dehydrogenase (U/l)	75-250	481	↑
Bilirubin (total, µmol/l)	0-17	26	↑
Troponin-I (µg/l)	0.00-0.04	1.18	↑
Creatine kinase-MB (µg/l)	0.0-7.0	1.7	
Endocrinology			
25 (OH) vitamin D (nmol/l)	50-250	5	↓
Parathyroid hormone (pmol/l)	1.5-7.6	84.3	↑

Figure 1A. *Electrocardiogram at presentation (calcium = 1.42 mmol/l)*

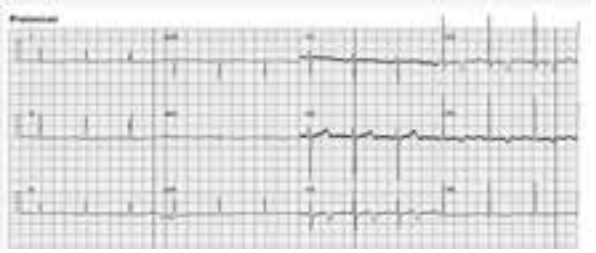
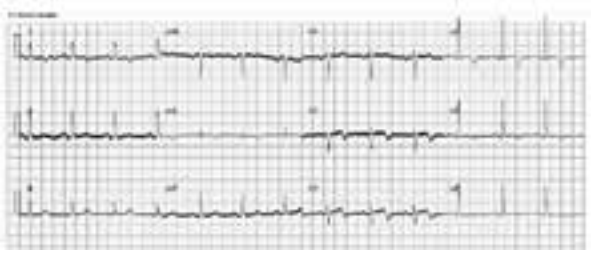


Figure 1B. *Electrocardiogram after calcium suppletion (calcium = 2.27 mmol/l)*



increased total bilirubin, lactate dehydrogenase levels and decreased haptoglobin levels compatible with chronic haemolysis. The leucocyte count was increased. The renal function was normal. The calcium level was very low at 1.42 mmol/l, while the albumin level was normal. Also the magnesium level was slightly decreased, but levels of the other electrolytes, including phosphate, were normal. The vitamin D level was low, whereas the parathyroid hormone level was high. Lastly, the marker of cardiac muscle tissue injury troponin-I was increased.

Electrocardiography showed a sinus rhythm of 74 beats/minute, an intermediate axis, normal PR and QRS conduction intervals, but a prolonged QTc time (525 msec). Furthermore, terminal negative T waves were observed in V3-V6, I and aVL (*figure 1*, upper panel); these abnormalities persisted after correction of serum calcium and nitrate administration (*figure 1*, lower panel). She did have relief of the chest pain upon nitrate administration. Echocardiography showed a non-dilated left ventricle with slight hypokinesia apical anterior (in agreement with the suspected area of ischaemia), but otherwise normal systolic and diastolic function. Right ventricular function was normal. During prolonged monitoring cardiac arrhythmias were not observed.

DIAGNOSIS

Chest pain due to myocardial ischaemia.

DISCUSSION

Considering the high oxygen extraction in the heart muscle and the fact that hypoxia promotes sickling of erythrocytes, the heart seems to be relatively protected from ischaemic damage in SCD. Yet, myocardial infarction is frequently found at autopsies.[11,23] Strikingly, atherosclerotic changes are usually absent. In one autopsy series, seven of 72 consecutive patients with SCD had myocardial infarction, but overt obstructive lesions were absent in all of them.[23] Cardiac ischaemia in SCD is rather caused by pathology at the level of the microvasculature and has a multifactorial aetiology. As in other vaso-occlusive crises, the process may be initiated by increased adherence of sickled erythrocytes to activated endothelium. Abnormally activated platelets and leucocytes sequestrate in the obstructed vessels and release inflammatory mediators. Haemolysis leads to the release of free haemoglobin which acts as an NO scavenger. Rheological changes due to hyperviscosity and structural changes of the microvasculature further add to the pathophysiology (reviewed by Voskaridou, et al.[20]). The recognition of cardiac ischaemia is hampered by the fact that chest pain in patients with SCD is often attributed to other causes. Furthermore additional diagnostic tests may not be discriminating either. Non-specific ST-T wave changes and signs of abnormal repolarisation are common electrocardiographic findings in SCD. Frequent intramuscular injection of analgesics may result in a rise in muscle enzymes which interferes with the interpretation with respect to myocyte damage. Lastly, in the absence of atherosclerotic lesions, coronary angiogram is typically normal.

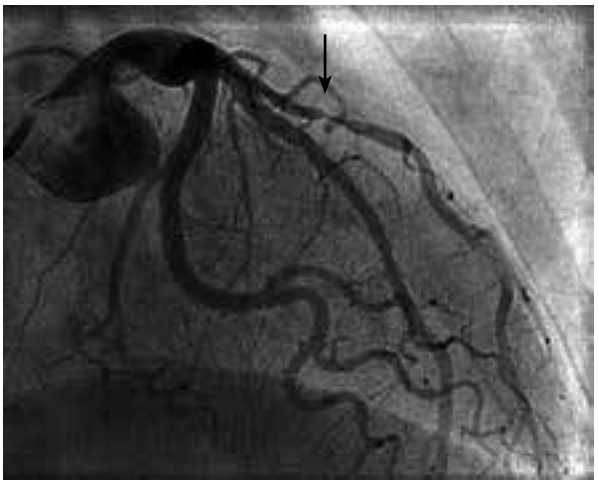
The muscle cramping is likely due to severe hypocalcaemia. Both calcium and high doses of colecalciferol were prescribed previously; however given the very low vitamin D level incompliance was suspected. The compensatory increased parathyroid hormone level supports the diagnosis of primary vitamin D deficiency.

The palpitations may indicate the presence of paroxysmal tachyarrythmias although not formally registered. Possible causes of tachyarrhythmias in this patient include anaemia, myocardial ischaemia, hypocalcaemia and (though less likely) torsade de pointes as complication of the prolonged QTc time (promoted by hypocalcaemia and methadone use).

EPILOGUE

Coronary angiography showed a subtotal stenosis (80-90%) in D1; the other coronary arteries appeared patent (*figure 2*). Although the pathophysiologies of atherosclerosis and vasculopathy of SCD have many overlapping features, previous cases of myocardial

Figure 2. *Coronary angiogram shows a subtotal stenosis in D1 (arrow), whereas the other arteries appear unaffected.*



infarction due to an atherosclerotic lesion have not been reported in patients with SCD. An important distinction between atherosclerosis and vasculopathy of SCD is the absence of atheromas in the latter, probably due to very low total cholesterol and LDL levels in patients with SCD.[24] Besides smoking cannabis, the patient had no risk factors for cardiovascular disease; however, evidence exists that low 25(OH) vitamin D levels are associated with an increased risk of cardiovascular disease.[25] Alternative causes for an isolated coronary stenosis, e.g. a congenital stenosis or muscular bridging, were unlikely based on the coronary angiography.

The patient was referred for percutaneous coronary intervention. A drug-eluting stent was placed via the arteria femoralis dextra. After this procedure the chest pain was relieved.

A thorough history revealed that the patient had stopped taking all the prescribed medication except for methadone many weeks ago. This explains why the serum calcium levels were very low despite high doses of colecalciferol and calcium.

Patients with SCD are vulnerable due to often extensive comorbidity and their increased risk for some common life-threatening conditions. This case illustrates the urgency to avoid preconceived opinions and the need to look beyond 'the usual suspects' in such patients presenting with acute pain.

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