SICKLE CELL ANEMIA: IMAGING FINDINGS OF THORACIC COMPLICATIONS

SUMMARY
Sickle cell anemia is an autosomal recessive disease characterized by rigid Red Blood cells (RBCs) that cannot pass through the capillaries of the tissue, and are destroyed and removed from circulation. The low deformity of the RBCs eases thrombus formation and vascular occlusion. Complications secondary to vascular thrombosis have the greatest clinical impact.

INTRODUCTION
Sickle cell anemia is a hemolytic anemia which is caused by a genetic mutation which causes glutamic acid to be exchanged with valine in the sixth position of the β chain of hemoglobin. When the hemoglobin of sickle cells (HbS) is de-oxygenated, it is relatively insoluble and has a high tendency to join with other chains which contain HbS, forming polymers which distort the erythrocyte and make them rigid. The sickle red blood cell easily adheres to the endothelium. Its capacity to become deformed and to pass through the capillaries is limited. For this reason, they occlude the capillaries and cause tissue ischemia (1-6). Sickle erythrocytes are destroyed and removed from circulation, which leads to anemia being generally well tolerated. However, complications secondary to vascular occlusion cause a greater clinical impact (1).

EPIDEMIOLOGY
This hereditary disease is an autosomal recessive disease which mainly affects the population groups with African, Indian, Arab, and Mediterranean backgrounds (7-9). In the United States, it is estimated that approximately 100,000 persons suffer from this condition. Life expectancy has increased due to advancements in therapeutic measures, with an average of 42 years of age for men and 48 years of age for women. However, the increase in life expectancy has also increased the incidence of chronic diseases in different organs (2,10,11).

ACUTE COMPLICATIONS

Acute thoracic syndrome
Defined as pulmonary opacities which recently appear on the thorax radiography, in a patient with a
background of sickle cell anemia who presents fever, thoracic pain, tachypnea and coughing (12-16). It is the most common cause of pulmonary disease in these patients and it is responsible for 25% of deaths. It occurs between 15-43% of this population and its frequency varies with age; in children, 24.5 yearly occur per each 100 patients per year while in adults, 8.8 yearly events occur per year. (2,17). Even though children are more prone to develop this condition than adults, adults have a higher mortality rate (4.3% vs 1.8%, respectively). The episodes are recurrent in up to 80% of cases. (18,19).

The mechanism which is responsible is still not completely understood. It is believed that it is a specific form of acute pulmonary lesion which may progress towards adult respiratory distress syndrome (SDRA). Pulmonary lesion is caused by several pathological processes which can coexist. It is often difficult to establish a specific cause (2).

There are different entities which cause acute thoracic syndrome. In the Multicenter Acute Chest Syndrome Study, performed by Vichinsky and collaborators, the following etiologies were found in 538 patients with sickle cell anemia who presented 671 episodes of acute thoracic syndrome: unknown cause (45.7%), pulmonary thromboembolism (16.1%), fat embolism (8.8%), infection due to Chlamydophila pneumoniae (7.2%), infection due to Mycoplasma pneumoniae (6.6%), viral infection (6.4%), typical bacteria (4.5%), and mixed infections (3.7%) (20).

Children with sickle cell anemia are 100 times as vulnerable to develop pneumonia than other children, given that their immunological system is seriously affected by autosplenectomy, the alteration of the phagocyte function and defects in opsonization. The recurrent rate of infections is 30% (19).

Pulmonary thromboembolism occurs due to the status of hyper-clotting of these patients (21). It can contribute to generate acute thoracic syndrome, as well as the development of chronic pulmonary disease, related to sickle cell anemia (2,22). Fat embolism is a consequence of bone infarcts. The diagnosis is confirmed with the bronchoalveolar lavage, which proves over 5% of lipid-filled macrophages (23-26).

One or multiple consolidation focal points can be found in thorax radiographies of patients with acute thoracic syndrome (figures 1, 2). Radiographies do not enable to differentiate if these consolidations are due to pneumonia or an infarct; in order to confirm an infarct, a thrombus in one of the branches of the pulmonary artery associated with a peripheral consolidation of triangular morphology must be proven in the computerized tomography (figure 3). Pleural effusion is common, even though it does not help differentiate the infectious causes from the non-infectious causes. (19,27).

It is frequent to find a mosaic perfusion pattern (figure 4). Bhalla and collaborators reported frosted glass areas due to areas of hemorrhagic edema, caused by irreversible ischemia or by excess perfusion (figure 2). When the consolidation focal points are observed, they more commonly reflect infarcts and less commonly reflect pneumonias (27,28). The imaging findings of fat embolism are non-specific and include diffuse alveolar opacities, areas of frosted glass, centrilobular and subpleural nodes which represent the alveolar edema, micro-hemorrhages and the secondary inflammatory response to ischemia (29) (figure 2).

**Cardiomegalia and pulmonary edema**

The increase in size of the cardiac silhouette in these patients is the result of the overload of volume which occurs after a vigorous hydric reanimation for the treatment of sickle-cell crises. It is more accentuated in patients who have a reduction in renal function due to micro-infarcts in the kidney. In addition to cardiomegalia, it is frequent to find a cephalization of pulmonary fluid with a subsequent development of septal lines. If the condition progresses, it results in the instauration of an alveolar pulmonary edema (30) (figure 5).
Figure 2. CT axial images of the thorax in the lung window of two patients who suffered from acute thoracic syndrome with a different etiology. A) 26-year old man with dyspnea. The CT showed frosted glass opacity and a consolidation in both inferior lobes. In addition, several centrilobular nodes were observed with a frosted glass density in the middle lobe. The imaging and clinical evaluation was consistent with an alveolar hemorrhage. B) 40-year old man with fever and coughing. The CT evidenced aerial space consolidations in both inferior lobes, consistent with the pneumonia clinical diagnosis.

Figure 3. Axial CT images with contrast medium. Patient hospitalized due to acute thoracic syndrome secondary to a pulmonary embolism. There is an acute thrombus in the artery for the right inferior lobe (white arrows), which extends towards a segmentary artery and causes a pulmonary infarct in the posterior basal segment (arrow heads).

Figure 4. Axial images in the lung window of the CT of the thorax. A subtle mosaic perfusion pattern (arrows) can be seen. This area presents smaller vessels, in lesser quantities than in the adjacent areas and in the right lung.
Chronic complications

Chronic pulmonary disease related to sickle cell disease.

The prevalence of this disease is unknown. There is a discrepancy in the information presented in the literature, given that some authors consider that approximately half of the patients present evidence of interstitial chronic pulmonary disease. However, others believe that only 4% of patients present this evidence (2.28%). It is characterized by imaging findings of pulmonary fibrosis, a moderate to serious deterioration of pulmonary function, and in its most serious form, by the development of pulmonary hypertension and cor pulmonale. It has been informed in young patients during their second decade of life. The prognosis is unfavorable given that death occurs approximately 7 years after diagnosis (2,31).

The main risk factors are the recurrent episodes of acute thoracic syndrome. Aquino and collaborators did a correlation between the severity and the extension of interstitial alterations in CT and the number of previous acute thoracic syndrome episodes (32).

The radiography of the thorax shows a generalized fine reticular pattern. A cardiomegalia is also observed, secondary to the increase of flow caused by anemia. Signs of pulmonary hypertension can be seen in severe cases.

The findings in the CT of the thorax show scars of repeated small pulmonary infarcts which lead to fibrosis. The following are included: bronchiectasis due to traction, thickening of the interlobular septa, parenchymal bands and the distortion of pulmonary architecture (figure 6). A honeycomb pattern is not usually found. The distribution of these alterations is patched up and predominantly basal. The permanent occlusion of pulmonary capillaries can develop pulmonary hypertension, which is imagingly manifested with the increase in the size of the main trunk of the pulmonary artery and with the hypertrophy of the right ventricle (19,28,33,34).

Pulmonary hypertension

Pulmonary hypertension is the most serious pulmonary chronic complication of sickle cell anemia. It has significant impact given that its mortality is high. Its prevalence ranges between 21-40% and it has even been documented in young children, starting from the age of 3 (2,35). The etiology of pulmonary hypertension in persons with sickle cell anemia is probably multi-factorial, caused by chronic hypoxemia, thrombosis in situ, reduction in the availability of nitric oxide, parenchymal and vascular lesion, fat embolism, chronic liver disease and asplenia. Once the pulmonary hypertension condition has been established, it becomes accentuated due to vascular occlusive episodes, exercise and hemolysis. (36,37).

The findings in the radiography of the thorax include an increase in the size of central pulmonary arteries, with amputation and loss of distal attenuation, as well as a cardiomegalia which is predominant in the right ventricle. The CT of the thorax shows an increase in the size of the main trunk of the pulmonary artery and in the segmentary arteries, related to the adjacent bronchus (loss of artery-bronchus ratio), as well as hypertrophy of the right ventricle, dilatation of the right atrium, and an attenuation mosaic perfusion pattern (30,36,38) (figure 7).

Cardiomegalia secondary to chronic anemia

The dilatation of the cardiac chambers and the hypertrophy of the left ventricle are secondary to high output cardiac failure which results from chronic anemia (39) (figure 8). Patients with levels of hemoglobin under 7 mg/dL present an increase of blood volume and develop a hyperkinetic hemodynamic status. This results in the fact that an increase in cardiac output favors the dilatation and hypertrophy of the myocardium. In the images, this translates into cardiomegalia (30,40,41).

Skeletal alterations in the thorax

Extramedullary hematopoiesis

Extramedullary hematopoiesis is a mechanism which produces red blood cells outside of the bone marrow, given that the bone marrow cannot supply the demand. Extramedullary hematopoiesis in the thorax is occasionally found in patients with sickle cell anemia (42,43).

Its pathogenesis is not clear. It has been suggested that it originates from the bone marrow which becomes herniated through the cortex of the ribs or the vertebrae. Homogenous masses are identified in the radiographies of the thorax. These masses are well defined, are located in the posterior mediastinum and are less frequently located in the intercostal spaces. The CT of the thorax enables a better characterization of these lesions; it also enables to identify unilateral or bilateral paravertebral masses, with soft tissue density, with well-defined shapes, sometimes lobulated, which do not erode the vertebral bodies or the ribs. In some occasions, they are associated with subpleural masses (42,44) (figure 9).
Figure 6. a) Radiography of the thorax, AP projection of a 24-year old male patient with a background of several acute thoracic syndrome episodes. This patient developed pulmonary fibrosis and cardiomegalia secondary to sickle cell anemia. Reticular interstitial opacities are disseminated in both lungs. B) CT of the thorax, lung window. The axial image shows a marked distortion of the pulmonary architecture, associated with bronchiectasis, frosted glass opacity and thickening of the intralobular and interlobular interstitium. Honeycomb areas are also identified in the left lung (arrow).

Figure 7. a) Radiography of the thorax, PA projection. There is an increase in the size of the main trunk of the pulmonary artery (black arrow). B) CT with contrast medium of the same patient. A marked precapillary pulmonary hypertension is confirmed (white arrow).

Figure 8. Radiographies of the thorax, frontal projections of two different patients with sickle cell anemia. A) Global cardiomegalia, and a pulmonary edema in the interstitial phase are identified. In this patient, cardiomegalia is a part of an acute condition of pulmonary edema. B) Refers to a different patient who presents cardiomegalia secondary to chronic anemia, without signs of cardiac failure.
H-shaped vertebrae

These are caused by infarcts of the vertebral plates, due to a microvascular occlusion. This occlusion, which is associated with an overgrowth of the adjacent secondary ossification centers, results in concave vertebral plates which confer the H-shaped vertebra appearance (47) (figure 10). A compensatory increase of the vertebra can also occur, which causes a deformity which has been described as tower vertebra (48–50).

Conclusion

Sickle cell anemia is a disease with a high rate of mortality and morbidity. It has numerous and frequent complications in the thorax. Due to this, radiologists must become familiar with these findings. Acute and chronic changes may coexist. Even though imaging findings are non-specific, the manifestations of these complications must be understood so that the radiologist can suggest a diagnosis.

References


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