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ABOUT COVER

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CASE REPORT

Central nervous system recurrence in a patient treated for acute promyelocytic leukemia, resulting in sideroblastic anemia: A case report

Haroon Nawaz, Ayesha Choudhry, William Joseph Morse

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Abstract

BACKGROUND

Previous cases that have been stated in this article have displayed that around 1% to 7% of patients that have been treated with chemotherapy for acute promyelocytic leukemia developed myelodysplastic syndrome or acute myeloid leukemia. One can see that's why this case presentation of a 60-year-old man that had a good response to acute promyelocytic leukemia treatment, that later presented with a central nervous system recurrence of acute promyelocytic leukemia and acquired sideroblastic anemia (a form of myelodysplasia) from treatment is a unique case report.

CASE SUMMARY

The presence of central nervous system relapse in acute promyelocytic leukemia patients is very unlikely compared to recurring mainly in the bone marrow. It is also uncommon to be diagnosed with sideroblastic anemia (form of myelodysplastic syndrome) as a result from treatment for acute promyelocytic leukemia. This case report highlights the detection, treatment/maintenance with idarubicin, all-trans-retinoic-acid, arsenic trioxide, methotrexate, 6-mercaptopurine, and ommaya reservoir intrathecal methotrexate administration in a patient that had central nervous system relapse of acute promyelocytic leukemia and acquired sideroblastic anemia.

CONCLUSION

In essence, first time relapse concerning the central nervous system in treated

acute promyelocytic leukemia patients who had a good response to therapy is very uncommon. The acquirement of a myelodysplastic syndrome such as ringed sideroblastic anemia is also rare regarding this patient population. Although such cases are infrequent, this case report represents a unique insight of the detection, treatment, and maintenance of a 60-year-old man diagnosed with acute promyelocytic leukemia, resulting in the acquirement of sideroblastic anemia and central nervous system relapse.

Key Words: Acute promyelocytic leukemia; Central nervous system relapse; Sideroblastic anemia; All-trans-retinoic acid; Myelodysplasia; Case report

Core Tip: Central nervous system recurrence and acquirement of sideroblastic anemia is a rare occurrence on their own and are even more unlikely to occur together in treated acute promyelocytic leukemia patients. We present a case presentation of a 60-year-old man that had a good response to acute promyelocytic leukemia treatment, that later presented with a central nervous system recurrence of acute promyelocytic leukemia and acquired sideroblastic anemia (a form of myelodysplasia) from treatment is a unique case report.

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INTRODUCTION

Acute promyelocytic leukemia is a form of acute myeloid leukemia that is mainly due to a translocation of chromosomes fifteen and seventeen that influence the expression of the promyelocytic leukemia/retinoic acid receptor alpha (*PML-RARA*) genes[1]. It has been noted that myeloid neoplasms related to treatment are more prevalent in solid tumors and lymphomas than compared to a myeloid neoplasm arising from acute myeloid leukemia (AML) or acute promyelocytic leukemia (APL). Denu *et al*[2] 2016 had shown that 1% to 7% of patients that were treated with chemotherapy for acute promyelocytic leukemia developed myelodysplastic syndrome or acute myeloid leukemia. In 1998, Liso *et al*[3] 1998 conducted a review of 120 patients treated with all-trans-retinoic acid (ATRA) and chemotherapy that were seen over a period of nine years at two different institutions. 7 out of the 120 patients were found to have extramedullary disease, but only one patient had disease in the central nervous system (CNS). Montesinos *et al*[4] 2009 conducted a study from 1996 to 2005 that had 739 acute promyelocytic leukemia (APL) patients who received induction therapy with ATRA and idarubicin, as well as consolidation chemotherapy for relapse. There were 11 patients that had confirmed central nervous system (CNS) relapse with a five-year cumulative central nervous system incidence of 1.7%. Latagliata *et al*[5] 2002 discovered that 6.5% of the 77 acute promyelocytic leukemia patients who had a complete response to induction and consolidation therapy acquired therapy-related myelodysplasia, acute myeloid leukemia, or a combination of the two in their study. One can see that's why this case presentation of a 60-year-old man that had a good response to acute promyelocytic leukemia treatment, that later presented with a central nervous system recurrence of acute promyelocytic leukemia and acquired sideroblastic anemia (a form of myelodysplasia) from treatment is a unique case report.

CASE PRESENTATION

Chief complaints

A 60-year-old white male comes into the hospital in 2009 with a complaint of blurred vision in his right eye (ophthalmologist noted occlusion of retinal vein), feeling somnolent, and weak for the past four weeks.

History of present illness

He was admitted to the emergency room for weakness, fatigue, and leukocytosis. The patient attributed his condition to a treated sinus infection he had prior. The patient presentation noted minor bruising

over the arms and legs, and no signs of bleeding episodes, such as, epistaxis, hematemesis, melena, or blood per rectum.

History of past illness

Sinus infection.

Personal and family history

Non-contributory.

Physical examination

Generalized weakness, fatigue, and leukocytosis. The patient attributed his condition to a treated sinus infection he had prior. The patient presentation noted minor bruising over the arms and legs, and no signs of bleeding episodes, such as, epistaxis, hematemesis, melena, or blood per rectum.

Laboratory examinations

White blood cell count of 41600, hemoglobin of 8.4, hematocrit of 23, platelet count of 20000, mean corpuscular volume of 93, segmented neutrophils percentage (seg %) of 2%, lymphocyte percentage of 6%, monocyte percentage of 3%, and absolute neutrophil count of 800. hemoglobin of 14, hematocrit of 39, white blood cell count of 9100, and platelet count of 130000. Three months later in 2020, the patient remained on maintenance low dose methotrexate and had improved blood counts that were a hemoglobin of 13, hematocrit of 40, white blood cell count of 7700, and platelet count of 158000. Hemoglobin of 14, hematocrit of 41, white blood cell count of 8600, and platelet count of 165000. Hemoglobin of 13, hematocrit of 39, white blood cell count of 7400, and platelet count of 157000.

Imaging examinations

Bone marrow biopsy of *PML-RARA* gene fusion by interphase fluorescent *in-situ* hybridization (Figure 1).

FINAL DIAGNOSIS

Central nervous system relapse of acute promyelocytic leukemia and acquired sideroblastic anemia (Figure 2).

TREATMENT

Idarubicin, ATRA, arsenic trioxide, methotrexate, 6-Mercaptopurine, and ommaya reservoir intrathecal methotrexate.

OUTCOME AND FOLLOW-UP

Patient has remained stable as of 2020, being manages with folic acid, thiamine, and pyridoxine.

DISCUSSION

One can determine that central nervous system recurrence and acquirement of sideroblastic anemia is a rare occurrence on their own and are even more unlikely to occur together in treated acute promyelocytic leukemia patients. From 1996 to 2008, Montesinos *et al*[6] 2010 analyzed therapy-related myeloid neoplasms in 1025 acute promyelocytic leukemia patients who received anthracycline-based chemotherapy and All-Trans-Retinoic acid. Seven out of the 918 patients that achieved a complete response had developed a therapy related neoplasm after a median of 43 mo from complete response: With a 6-year cumulative incidence of therapy-related myeloid neoplasm of 2.2 %. From 1991 to 1998 Lobe *et al*[7] 2003 dealt with treating 677 newly diagnosed acute promyelocytic leukemia patients. Six hundred and seventeen out of the 677 patients achieved a complete response with combination All-Trans-Retinoic acid and chemotherapy; 246 acute promyelocytic leukemia patients had received maintenance chemotherapy, 6-mercaptopurine, and methotrexate. At the median 51-month follow-up, 0.97% of the treated acute promyelocytic leukemia patients developed myelodysplastic syndrome. De Botton *et al*[8] 2006 discovered that 23% of patients relapsed after obtaining a complete response, and about 5% had a 3-year cumulative incidence for first time central nervous system relapse. The study analyzed potential risk factors for central nervous system relapse: age less than 45 years-old (P = 0.05),

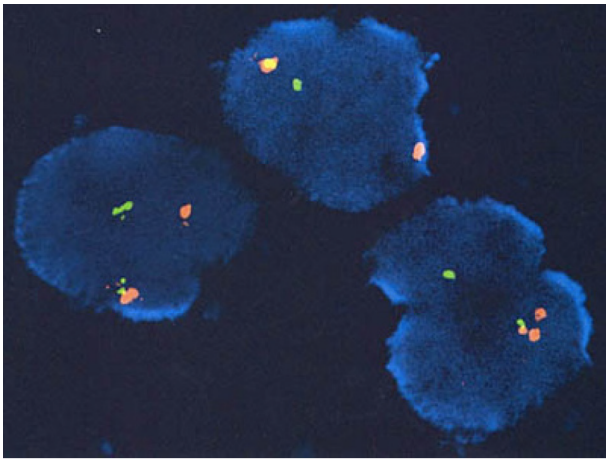

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Figure 1 Bone marrow biopsy of promyelocytic leukemia/retinoic acid receptor alpha gene fusion by interphase fluorescent *in-situ* hybridization.

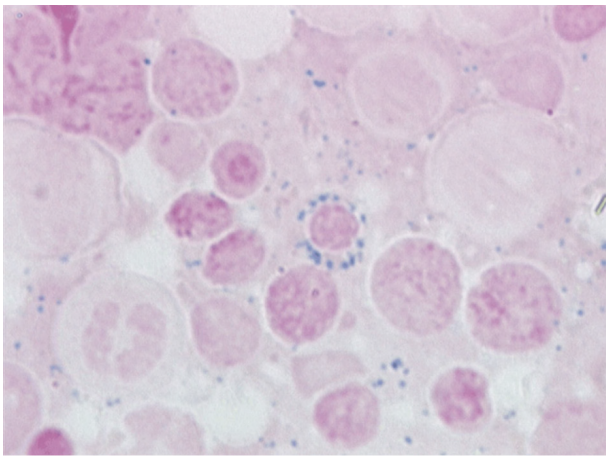

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Figure 2 Bone marrow biopsy and iron staining displaying sideroblastic anemia.

bcr3 PML-RAR-alpha isoform (P = 0.0003), and a white blood cell count greater than or equal to 10000/mm^3. Specchia *et al*[9] 2001 enrolled patients into two trials that were designed to see if there was any difference in extramedullary disease at relapse regarding combination All-Trans-Retinoic acid and chemotherapy compared to solely chemotherapy. It was discovered that the All-Trans-Retinoic acid plus chemotherapy and solely chemotherapy arms had 0.6% and 2%, respectively. These previous cases highlight the rarity of an acute promyelocytic leukemia patient acquiring central nervous system relapse as well as myelodysplastic syndrome, which make this case report relevant for future treatment applications pertaining to this patient population.

CONCLUSION

In essence, first time relapse concerning the central nervous system in treated acute promyelocytic leukemia patients who had a good response to therapy is very uncommon. The acquirement of a myelodysplastic syndrome such as ringed sideroblastic anemia is also rare regarding this patient population. Although such cases are infrequent, this case report represents a unique insight of the detection, treatment, and maintenance of a 60-year-old man diagnosed with acute promyelocytic leukemia, resulting in the acquirement of sideroblastic anemia and central nervous system relapse.

FOOTNOTES

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CASE REPORT

Efficacy of HA330-II column hemoadsorption in Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis combined with liver failure: A case report

Qian Gao, Xiao-Wei Xin, Chun Zhao, Yu-Juan Wang, Wei Wang, Yi Yin, Xiao-Ru Wang, You-Peng Jin

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Abstract

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a severe and potentially deadly condition associated with extensive inflammation and immune activation. Cytokine adsorption may serve as a supportive treatment that can stabilize organ function in affected patients by reducing their circulating cytokines levels. To date, no descriptions of clinical experiences associated with the use of HA330-II column hemoadsorption for the treatment of children affected by HLH have been published.

CASE SUMMARY

We describe the case of an 11-year-old child with Epstein-Barr virus-associated HLH complicated by liver failure. She underwent HA330-II column hemoadsorption and chemotherapy and exhibited reductions in levels of inflammatory cytokines, including interleukin (IL), IL-6, IL-8, IL-10, and interferon-γ. The patient's condition and laboratory parameters gradually improved with treatment.

CONCLUSION

Hemoadsorption may play an important role in cytokine storm elimination in children with HLH combined with liver failure and consequent multiple organ failure.

Key Words: Hemoadsorption; HA330-II column; Hemophagocytic lymphohistiocytosis; Pediatric; Liver failure; Case report

Core Tip: Hemophagocytic hymphohistiocytosis (HLH) is an often fatal disease. We report an 11-year-old female who was diagnosed with Epstein-Barr virus-HLH and presented with coagulation disorders, liver damage, and respiratory insufficiency. In the present case, initially elevated interleukin (IL)-6, IL-8, IL-10, and interferon-γ levels were reduced to within normal ranges following hemoadsorption with HA330-II, and the patient's condition gradually improved. HA330-II hemoadsorption has the ability to bridge the patient until chemotherapy can contribute to reduced HLH disease activity.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe and potentially lethal disorder associated with excessive inflammation and unrestrained immune activation[1]. Patients with HLH exhibit dramatically elevated levels of cytokines, including interleukin (IL)-1, IL-2, IL-6, IL-18, tumor necrosis factor-α, and interferon (IFN)-γ[2]. HLH is classified into two groups: Primary and acquired. Primary HLH primarily develops as a consequence of genetic defects during infancy, while acquired HLH occurs in the context of auto-inflammatory/autoimmune diseases, lymphoma, or certain viral infections, with Epstein-Barr virus (EBV) being a common cause. Animal studies[3,4] and case series have demonstrated that a reduction in circulating cytokine levels achieved *via* hemoadsorption can be effective as a treatment for HLH[5,6]. HA330-II perfusion columns have been reported to be capable of absorbing multiple inflammatory factors and have been successfully used as a component of a double plasma molecular adsorption system to treat patients suffering from liver failure[7,8]. In the present article, we describe one case of a child diagnosed with EBV-associated HLH combined with liver failure who successfully underwent HA330-II column hemoadsorption and chemotherapy treatment. Through these treatments, the patient's condition improved and her recovery was satisfactory.

CASE PRESENTATION

Chief complaints

An 11-year-old female was admitted to our hospital with a 5 d history of high fever with chills and a headache as well as damaged liver function. She did not exhibit a cough, abdominal pain, or vomiting.

History of present illness

Before this visit, she had been given a penicillinase antibiotic for 3 d and azithromycin for 1 d. Her clinical state rapidly deteriorated, and she developed respiratory failure, capillary leak syndrome, and hypotension. As such, she was admitted to the pediatric intensive care unit.

History of past illness

The patient had a history of encephalitis 3 years ago, and she had recovered after treatment for 2 wk.

Personal and family history

This patient had no specific personal or family history.

Physical examination

On initial examination, the patient had a fever with a maximal temperature of 40.0 °C, a respiratory rate of 30 breaths per min, a heart rate of 122 bpm, and a blood pressure of 82/41 mmHg at admission. She was in a poor mental state and presented with jaundice and hepatosplenomegaly. Other physical examinations were normal.

Laboratory examinations

Initial laboratory studies in the pediatric intensive care unit revealed excessive hyperferritinemia (58360

ng/mL, reference range: 11.0-306.8 ng/mL), low natural killer cell activity (0.32%, reference range: 5%-26%), hypofibrinogenemia (0.84 g/L, reference range: 1.50-4.35 g/L), leukopenia (2.07 × 10^9/L, reference range: 3.5-9.5 × 10^9/L), neutropenia (0.92 × 10^9/L, reference range: 1.8-6.3 × 10^9/L) elevated international normalized ratio values (1.92, reference range: 0.8-1.2), thrombocytopenia (42 × 10^9/L, reference range: 125-350 × 10^9/L), elevated alanine transaminase (ALT) levels (921 U/L, reference range: 7-40 U/L), aspartate aminotransferase (AST) levels (2223 U/L, reference range: 13-35 U/L), and elevated total bilirubin (TBIL) levels (108.7 mmol/L, reference range: 3.5-23.5 mmol/L). The patient also exhibited high levels of C reactive protein (76.40 mg/L, reference range: 0-8 mg/L), procalcitonin (2.73 ng/mL, reference range: 0-0.05 ng/mL), IL-6 (154.06 pg/mL, reference range: 0-5.4 pg/mL), IL-8 (32.67 pg/mL, reference range: 0-20.6 pg/mL), IL-10 (169.81 pg/mL, reference range: 0-12.9 pg/mL), and IFN-γ (4387.41 pg/mL, reference range: 0-23.1 pg/mL). EBV-DNA loads were also found to be significantly elevated (3.82 × 10^6 copies/mL). Multiple blood and sputum cultures as well as the other viral polymerase chain reaction tests for common respiratory viruses and cytomegalovirus were all negative. A bone marrow biopsy revealed the presence of hemophagocytosis.

Imaging examinations

A thoracic-abdominal computer tomography analysis revealed pulmonary inflammation and no evidence of tumors.

FINAL DIAGNOSIS

She was diagnosed with EBV-associated hemophagocytic syndrome combined with liver failure in accordance with the HLH-2004 guidelines[9].

TREATMENT

Treatment with meropenem, norepinephrine, intravenous immunoglobulin, ganciclovir, and dexamethasone as well as high-flow nasal cannula placement were initiated. However, these approaches were ineffective as evidenced by sustained fever, hypoxemia, and hypotension. Chemotherapy was recommended for the patient, but her parents refused and asked for other therapeutic options. In light of the refractory state of her HLH and her poor general condition, we next sought to achieve the immediate suppression of hypercytokinemia. Accordingly, we initiated blood purification. Plasma exchange was initially considered but could not be performed owing to reduced plasma separator access due to the coronavirus disease 2019 pandemic. As such, we tried to perform hemoadsorption (HA330-II perfusion column, Zhuhai Health Sails Biotechnology Co., Ltd., Zhuhai, China) in this patient. Informed written consent was obtained from the patient's parent. Heparin sodium was employed for anticoagulation, and the patient was infused with platelets and fibrinogen prothrombin complex concentrate.

On the 1st day of hospitalization, she was in poor condition with respect to her clinical symptoms and biochemical parameters. She also needed a high dose of norepinephrine to maintain appropriate cardiovascular function. On the 2nd day of hospitalization, one round of the above mentioned hemoadsorption strategy was implemented. This hemoadsorption approach was implemented two more times over a 3-d period. On the 5th day of hospitalization, the patient exhibited significantly decreased levels of IL-6 (12.16 pg/mL), IL-8 (10.63 pg/mL), IL-10 (63.38 pg/mL), and IFN-γ (61.99 pg/mL) (Figure 1). She was gradually weaned off norepinephrine treatment, and her fever disappeared while her total leukocyte and neutrophil counts increased. However, no significant improvement in liver function was observed (ALT 766 U/L, AST 1196 U/L, TBIL 170.54 mmol/L, Fib 1.23 g/L), and inflammatory markers rebounded after hemoadsorption had been discontinued for 2 d, at which time the patient again developed a fever that reached as high as 40.0 C. At that time, her parents provided consent for chemotherapy (HLH-2004) treatment (Figure 2), which was initiated in combination with hemoadsorption.

OUTCOME AND FOLLOW-UP

The hemoadsorption approach was implemented an additional three times over a 5-d period, and the patient's condition gradually improved. On the 13th day of hospitalization, decreased levels of IL-10 (30.06 pg/mL) and IFN-γ (50.69 pg/mL) (Figure 1), improved liver function (ALT 257 U/L, AST 393 U/L, TBIL 79.91 mmol/L, Fib 1.45 g/L) (Figure 3), and increased platelet counts were all evident. She was discharged on the 40th day after admission owing to her good recovery status. The patient underwent an additional 30 d of chemotherapeutic treatment without significant adverse events. Furthermore, no disease recurrence was evident as of 8 mo post-discharge.

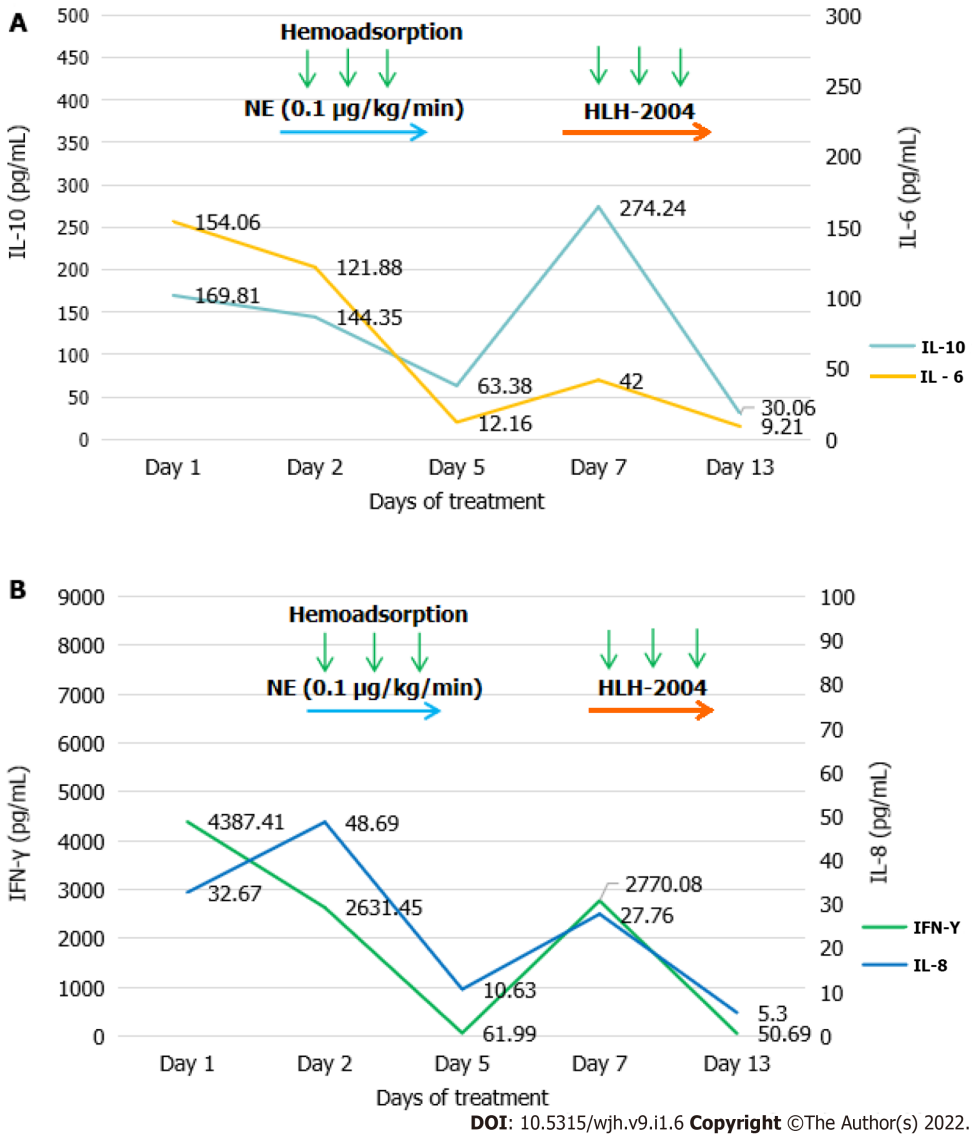

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Figure 1 Interleukin 6 and interleukin 10 levels, and interferon-γ and interleukin 8 levels under treatment during the first 13 d after pediatric intensive care unit admission. A: Interleukin 6 and interleukin 10 levels; B: Interferon-γ and interleukin 8 levels. IL: Interleukin; NE: Norepinephrine; HLH: Hemophagocytic lymphohistiocytosis; IFN: Interferon.

DISCUSSION

HLH is an often fatal disease, and affected patients typically present with high-grade fever, progressive hypocytosis, liver dysfunction, and coagulopathy[9]. In our case, the patient presented with a persistent fever that had been present for more than 1 wk, hypocytosis, hypofibrinogenemia, splenomegaly, hyperferritinemia, and lymphohistiocytic accumulation in the bone marrow. HLH was thus diagnosed in this child. The most common treatment for HLH at present is chemotherapy[9]. However, when patients also present with serious organ damage, chemotherapy may not work, as the existence of severe multiorgan failure at presentation can lead to a high mortality rate[10]. At admission, our patient was in poor condition and presented with coagulation disorders, liver damage, and respiratory insufficiency. In such a context, cytokine adsorption has the potential to bridge the patient until chemotherapy can contribute to reduced HLH disease activity[5].

The primary pathophysiological characteristics of HLH include excessive cytotoxic T cell and macrophage activation and expansion. These activated immune cells, in turn, produce excessively high levels of inflammatory cytokines, including IL-1, IL-2, IL-6, IL-10, TNF-α, and IFN-γ, which can promote further cytotoxic T cell and macrophage activation and expansion, thereby exacerbating the ongoing cytokine storm and driving consequent multiple organ failure[2]. On admission, patients present with increased circulating levels of certain inflammatory cytokines, such as IL-6, IL-8, IL-10, and IFN-γ, suggesting an ongoing systemic inflammatory reaction. HA330-II is a neutral microporous resin column with abundant micropores and a high specific surface area[11]. HA330-II cartridges have the ability to adsorb medium and large-sized inflammatory cytokines, including those of the IL and TNF families. In

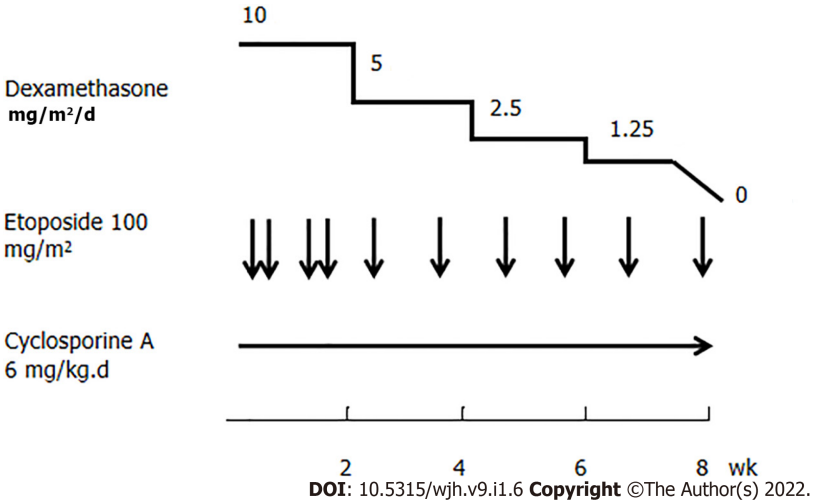

Figure 2 Chemotherapy protocol for the treated patient.

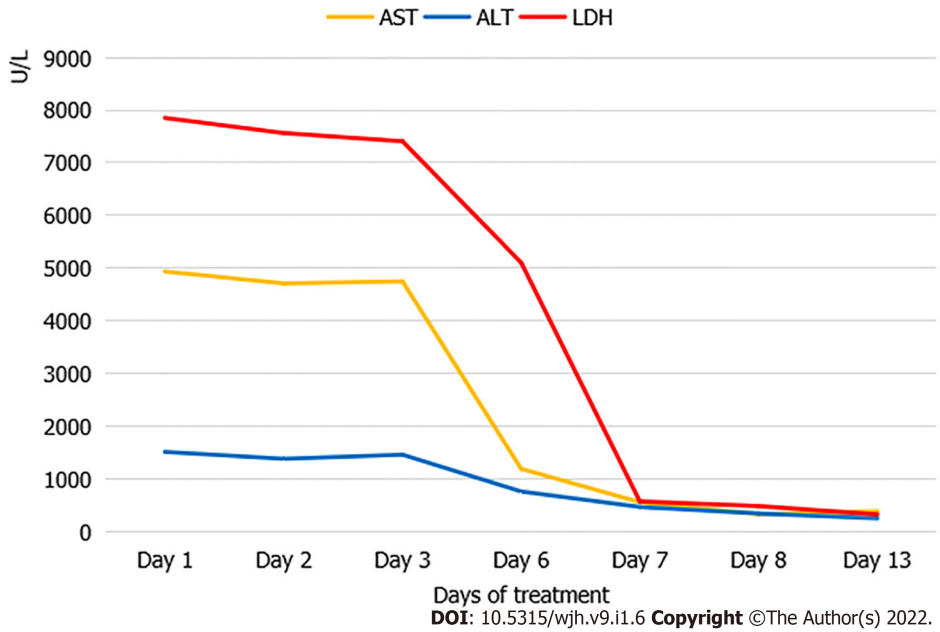

Figure 3 Changes in laboratory values during the first 13 d after pediatric intensive care unit admission. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase.

the present case, initially elevated IL-6, IL-8, IL-10, and IFN-γ levels were reduced to within normal ranges following hemoadsorption with HA330-II. This indicated that this column was able to reduce effectively inflammatory cytokines levels in our treated patient. However, this approach was unable to remediate effectively HLH-related liver failure in this patient, whereas hemoadsorption combined with chemotherapy was found to be more effective than hemoadsorption alone.

With respect to hemoadsorption, the CytoSorb™ column or endotoxin-binding polymyxin B-immobilized fiber column hemoadsorption approaches have also been reported for the treatment of HLH[12,13]. Cytokine adsorption associated with the CytoSorb™ column results in an improvement in the condition of treated patients, thus aiding in achieving symptom relief in affected individuals. Polymyxin B-immobilized fiber columns have also contributed to the recovery of circulatory dynamics associated with HLH. Several recent studies have demonstrated that HA330-II hemoadsorption plays a critical part in the elimination of inflammatory cytokines[14,15]. To the best of our knowledge, this is the first report to describe the clinical application of an HA330-II perfusion column in children suffering from HLH. However, as this is a report of outcomes for a single patient, large-scale trials will be necessary to investigate the clinical indications for such hemoadsorption treatment.

CONCLUSION

In summary, for EBV-associated HLH, HA330-II column-mediated hemoadsorption can safely reduce the levels of circulating inflammatory cytokines, serving as a beneficial and essential supplement to chemotherapy.

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FOOTNOTES

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CASE REPORT

Late ischemic stroke and brachiocephalic thrombus in a 65-year-old patient six months after COVID-19 infection: A case report

Kristen Jane Kilby, Catherine Anderson-Quiñones, Keith Richard Pierce, Kirollos Gabrah, Ankur Seth, Allison Brunson

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Abstract

BACKGROUND

Although it is well established that coronavirus disease 2019 (COVID-19) is associated with inflammation and a prothrombotic state leading to stroke and venous thromboembolism (VTE), the nuances of this association are yet to be uncovered[1]. Many studies link elevations in inflammatory markers to cases of thromboembolism. Most reports of thromboembolism associated with COVID-19 occur in the venous circulation during or just after the initial hospitalization due to COVID-19[2]. It is unclear how long the hypercoagulable effect of COVID-19 lasts.

CASE SUMMARY

We present a unique case of a 65-year-old-female who presented to her primary care doctor with a sore throat, cough, fatigue, congestion, diarrhea, headache, and anosmia. She tested positive for severe acute respiratory syndrome coronavirus 2 and received a bamlanivimab infusion 9 days later. After recovering from the acute illness, she received the Pfizer-BioNTech COVID-19 vaccine. Months later, she presented to the Emergency Department (ED) complaining of right sided shoulder pain and motor weakness in her left hand while trying to type on a keyboard. On presentation to the ED, her calculated Padua prediction score for risk of VTE was two and inflammatory markers were not elevated. She was found to have a brachiocephalic artery occlusion as well as an ischemic stroke which was treated with heparin.

CONCLUSION

This case suggests hypercoagulability due to COVID-19 may extend further than current literature suggests, to at least six months.

Key Words: COVID-19; Stroke; SARS-CoV-2; Thrombus; Vaccine; Case report

Core Tip: Acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with hypercoagulability. However, in this unique case, a patient suffered two separate thromboembolisms, one in the brachiocephalic artery and an ischemic stroke. With only two risk factors at baseline and no corresponding elevation in inflammatory markers, we hypothesize that the clots grew slowly over time which would not cause acutely elevated inflammatory markers. Although her SARS-CoV-2 infection occurred six months prior to her Emergency Department presentation, we hypothesize the hypercoagulable state caused by coronavirus disease 2019 was contributory. Additionally, it is unlikely the vaccination alone caused her thrombosis, yet it is still possible it had a contributory effect.

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INTRODUCTION

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimer[1,3]. It is common for hospitalized SARS-CoV-2 positive patients to receive higher than usual prophylactic doses of anticoagulants due to the established association between coronavirus disease 2019 (COVID-19) and thromboembolism[4]. However, when patients are not admitted to the hospital, they typically do not receive anticoagulation therapy unless there is another indication. Rivaroxaban can be used for venous thromboembolism (VTE) prophylaxis for acutely ill medical patients. For this indication, it is administered orally as a 10 mg dose once daily for 31 to 39 days (including hospitalization and post-discharge)[5,6]. Some providers consider using rivaroxaban in this way for high-risk COVID-19 patients who are discharged from the hospital. The International Society on Thrombosis and Haemostasis confirms it is "reasonable to consider extended-duration thromboprophylaxis with low molecular weight heparin or a direct oral anticoagulant for at least two weeks and up to six weeks post-hospital discharge in selected COVID-19 patients who are at low risk for bleeding and with key VTE risk factors such as advanced age, stay in the Intensive Care Unit, cancer, a prior history of VTE, thrombophilia, severe immobility, an elevated D-dimer, and an IMPROVE VTE score of four or more[7]." We present a case of a 65-year-old-female who was not hospitalized for her SARS-CoV-2 infection and six months (197 days) later presented to the hospital with a thrombus in the brachiocephalic artery and an acute ischemic stroke in the right anterior cerebral artery (ACA)/middle cerebral artery (MCA) watershed region with no apparent inciting factors.

CASE PRESENTATION

Chief complaints

A 65-year-old-female presented to the Emergency Department (ED) complaining of right sided shoulder pain and motor weakness in her left hand while trying to type on a keyboard. In the ED, she experienced worsening left upper extremity weakness which improved after one hour.

History of present illness

The patient's symptoms began after waking up and had a sudden onset.

History of past illness

The patient has a past medical history of depression, anxiety, asthma, gastroesophageal reflux disease, and iron deficiency anemia. She had no prior history of right arm, shoulder, or clavicular injury on the

right upper extremity. She tested positive for SARS-CoV-2 six months (197 days) prior to hospital presentation. After testing positive, she presented to her primary care doctor with a three-day history of fever (38.6 °C), sore throat, cough, fatigue, congestion, diarrhea, headache, and anosmia. Nine days following COVID-19 symptom onset, she received a bamlanivimab infusion through the left antecubital vein in an outpatient setting due to unrelenting symptoms. She became afebrile two days after the infusion and presenting symptoms remitted. She did not require hospitalization during her acute infection with COVID-19. After recovering from the acute illness, she received her first and second dose, 103 and 124 days later, respectively, of the Pfizer-BioNTech COVID-19 vaccine (0.3 mL) in the left deltoid. Both vaccinations caused soreness in the left arm, but no other adverse effects were reported after vaccination. The second vaccination occurred two and a half months (73 days) prior to her presentation to the ED. There was no period of upper limb immobilization.

Personal and family history

The patient reported having a normal colonoscopy about six years prior and a mammogram three years prior. No pap smear or pelvic exam in the last few years was reported. The patient is unaware of any family or personal history of blood clots.

Physical examination

Physical exam was significant for localized motor weakness and hyperreflexia in the left arm, and slight decreased sensation to light touch in her left foot. The National Institutes of Health Stroke Scale score was one with right arm drift. The calculated HAS-BLED score was zero indicating no contraindication to anticoagulation.

Laboratory examinations

Inflammatory markers were not elevated on admission or throughout her hospital stay. During the hospital admission, inflammatory markers were as follows: Erythrocyte Sedimentation Rate (ESR) 2 mm/hr, Troponin < 0.04 ng/mL, C-reactive protein (CRP) < 3 mg/L, Ferritin 4 ng/mL, Lactate Dehydrogenase 161 U/L, D-Dimer < 0.27 ug/mL. Pro B-Type Natriuretic Peptide (ProBNP) and Procalcitonin were not performed during this hospital admission. The SARS-CoV-2 ribonucleic acid rapid test collected on admission was negative. A lipid panel revealed elevated cholesterol (235 mg/dL) and low-density lipoprotein (129 mg/dL).

Imaging examinations

Brain magnetic resonance imaging showed subacute multifocal embolic appearing infarcts in the MCA watershed extending from anterior to posterior with involvement of the right hand knob and motor strip distribution (Figure 1).

The Head and Neck Computed Tomography (CT) Angiogram found a non-occlusive filling defect in the right proximal brachiocephalic artery (Figure 2).

Further diagnostic work up

To determine the cause of the stroke, a transthoracic echocardiogram (TTE) and a transesophageal echocardiogram were performed. Testing showed normal heart function with an ejection fraction of 60 to 65% and no patent foramen ovale.

FINAL DIAGNOSIS

The final diagnosis of the presented case is a thrombus in the brachiocephalic artery and an acute ischemic stroke in the right ACA/MCA watershed region.

TREATMENT

The patient was started on a heparin drip at 12 units/kg/h which was adjusted as necessary to maintain an activated partial thromboplastin time between 85 and 107 s. Oral aspirin 325 mg was administered and then transitioned to 81 mg daily. No tissue plasminogen activator (TPA) was given, as she was outside of the TPA administration window. Heparin was discontinued and apixaban 5 mg twice daily was started after a repeat Head and Neck CT Angiogram was normal.

OUTCOME AND FOLLOW-UP

To rule out malignancy related hypercoagulability, a colonoscopy and mammogram were

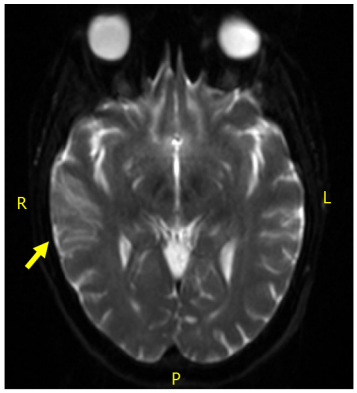

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Figure 1 Diffusion-weighted magnetic resonance imaging of right middle cerebral artery watershed embolic infarct.

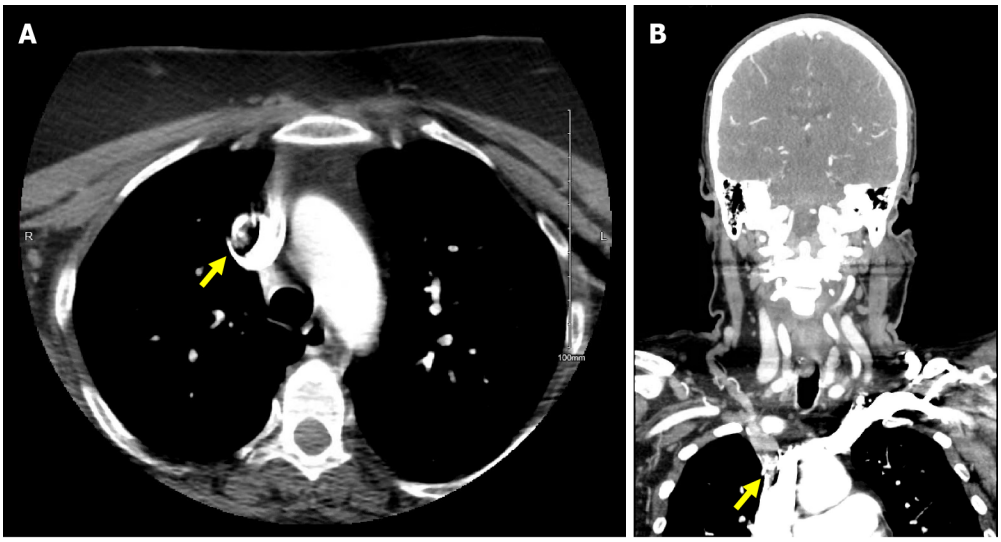

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Figure 2 Computed tomography image. A: Head and Neck computed tomography angiogram in transverse section with filling defect noted in base of proximal right brachiocephalic artery. B: Computed tomography angiogram in coronal section with filling defect noted in base of proximal right brachiocephalic artery.

recommended outpatient after discharge.

At discharge, new medications for the patient included aspirin 81 mg daily, apixaban 5 mg twice daily and atorvastatin 40 mg daily.

DISCUSSION

COVID-19 is associated with an increased risk of thromboembolism. It has been related to venous thrombosis more frequently than arterial thrombosis[8]. Many recent studies have concluded that thromboembolisms related to a SARS-CoV-2 infection are commonly accompanied by elevated inflammatory markers. A study by Guan and colleagues found disease severity was associated with elevated CRP (≥ 10 mg/L). Eighty-one and a half percent (110/135) of severe cases *vs* 56.4% (371/658) of non-severe cases presented with elevated CRP ($P < 0.001$)[9]. Similarly, three studies from China found CRP was elevated in patients with COVID-19 and linked to severity of disease[10-12]. Elevated ferritin levels have also been associated with severity[10,13]. In a prospective study, D-dimer, fibrinogen, and fibrin degradation product (FDP) levels were higher in patients with COVID-19, compared to healthy controls ($P < 0.001$ for all three comparisons). Higher values of D-dimer and FDP were seen in patients with more severe disease than in those with milder manifestations ($P < 0.05$ for both comparisons)[1]. Several studies have found D-dimer elevated in patients with COVID-19 and associated with worse outcomes [10,12-15]. In the unique case presented here, the patient's thromboembolisms did not follow the typical presentation because there was no corresponding elevation in inflammatory markers and the timing of the thromboembolism was well outside the reported time frame of the post COVID-19 infection period.

One possible explanation for this, is that the clots grew slowly over time which would not cause acutely elevated inflammatory markers.

It is also important to consider the patient's risk factors for a thromboembolism. History of a VTE, malignancy, age greater than 50, venous stasis, vascular injury, medications such as estrogen, and a hypercoagulable state can all increase a patient's risk for thromboembolism. At baseline, our patient was independently performing activities of daily living. Her established risk factors include her age (65 years) and her BMI of 30.45 which is categorized as obese. Her calculated Padua score at the time of COVID-19 onset was two (obesity and acute illness). On presentation to the ED six months later, her calculated Padua prediction score for risk of VTE was two (obesity and acute ischemic stroke). During admission, it increased to five due to reduced mobility. Because her Padua score was less than four there was no indication to initiate VTE prophylaxis until she was admitted to the hospital. She suffered two separate embolisms with only two risk factors at baseline, leading us to hypothesize that her recent SARS-CoV-2 infection caused a hypercoagulable state which led to her hospital admission.

We cannot however rule out the potential impact of the bamlanivimab infusion or Pfizer-BioNTech COVID-19 vaccination on her coagulable state. Administration of the Johnson & Johnson/Janssen vaccine was temporarily paused due to several reports of thrombosis. It has since been resumed as these events were determined to be very rare, especially above age 50. The combined incidence of thrombosis from at least one dose of the Pfizer or Moderna vaccines in women less than 50 years old was one case per 222951 vaccinated. The median time-to-event was three days[16]. Incidence in older women is not well defined. Both 0.3 mL doses of the Pfizer-BioNTech COVID-19 vaccine were administered to the left deltoid and after each vaccination, the left arm became sore. Given this information, it is unlikely the vaccination alone caused her thrombosis, yet it is still possible it had a contributory effect. Additionally, she received a bamlanivimab infusion. Bamlanivimab is not reported to cause or be associated with increased risk of thrombosis but there is not a lot of data on the long-term effects yet. Therefore, we do not believe this infusion played significantly into this patient's clinical course aside from decreasing her likelihood of being hospitalized at the time of her SARS-CoV-2 infection. Many proposed mechanisms for the association of SARS-CoV-2 infection and hypercoagulability stem from endothelial injury that leads to an inflammatory response. It is unclear how long the hypercoagulability associated with COVID-19 lasts. A case report described three critically ill SARS-CoV-2 positive patients who each suffered multiple cerebral infarctions. These patients ranged from 65 to 70 years old; similar to the patient presented in our case. Their thrombotic event occurred 10, 18, and 33 days from disease onset [17]. This case report suggests COVID-19 associated hypercoagulability may last beyond that timeframe. The case we have presented here suggests hypercoagulability may extend even further beyond this period as the thromboses occurred six months after a SARS-CoV-2 infection.

CONCLUSION

The sequelae of COVID-19 are numerous and are associated with significant complications, one of which is thromboembolism. Without a more complete understanding of this disease process, determining appropriate prognostic indicators and therapeutics has yet to be fully elucidated. In this case report, we discussed a patient who presented with a serious and unexpected complication possibly related to a SARS-CoV-2 infection months prior. Larger case series and cohort studies are needed to determine if the presentation described in this case report has been observed in other patient populations. These additional studies will allow for better understanding of the risks associated with prolonged hypercoagulability in the setting of COVID-19.

FOOTNOTES

Author contributions: Anderson-Quiñones C and Seth A were the patient's hospitalists, reviewed the literature and contributed to manuscript drafting; Kilby KJ, Gabrah K, and Pierce KR contributed to manuscript drafting; Brunson A was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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SYSTEMATIC REVIEWS

Cardiopulmonary changes in patients with sickle cell anemia: A systematic review

Jamile Silva Lopes, Ícaro Garcia Viana, Maria Luísa Cordeiro Santos, Fabrício Freire de Melo, Márcio Vasconcelos Oliveira, Cláudio Lima Souza

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Abstract

BACKGROUND

Given the high prevalence of cardiovascular and pulmonary abnormalities associated with sickle cell anemia (SCA), the clinical impact caused in addition to compromising the quality of life of patients and the overcharge that it represents to the public health system, this study systematized and evaluated scientific publications on pulmonary complications and cardiovascular diseases in sickle cell patients from 1920 to 2020. This compilation aims to provide knowledge for health professionals and managers in order to draw attention to the importance of chronic diseases in SCA patients and in addition to providing elements that provide improvements in management of useful resources that contribute to improve the quality and increase the life expectancy of these patients.

AIM

To systematically compile information about cardiopulmonary changes in patients with SCA.

METHODS

A systematic literature review was performed based on the PRISMA recommendation including scientific articles indexed in the Scientific Electronic Library Online databases of the United States National Library of Medicine and Biblioteca Virtual de Saúde. The search period was delimited between 1990 and 2020 and selected in Portuguese, English and Spanish. Three sets of descriptors were used for each database including research carried out with human beings. After reading the articles, those useful for this review were extracted using a collection instrument designed for this purpose.

RESULTS

The final selection included 27 studies. The year with the highest number of

publications was 2016 with 5 studies (18.51%), followed by 2017 with 4 (14.81%). The type of study most carried out in the period was cohort 10 (37.03%) followed by cross-sectional and case-control with 8 studies in each (29.62%). Regarding the language of publication, the distribution was as follows: 25 (92.59%) in English, 1 (3.70%) in Spanish and 1 (3.70%) in Portuguese.

CONCLUSION
The findings of the present study suggest that cardiopulmonary alterations represent a serious clinical repercussion of SCA. Of the analyzed studies, the high occurrence of pulmonary hypertension, ventricular hypertrophy and diastolic dysfunction stands out as the main cardiopulmonary complications. In view of the increased survival in SCA, there is a need for surveillance and the development of strategies aimed at preserving the cardiopulmonary function and consequently improving the quality of life of these patients.

Key Words: Sickle cell anemia; Cardiopulmonary alterations; Clinical profile; Systematic review

Core Tip: Sickle cell anemia (SCA) is the most common and severe form of sickle cell disease (SCD) accounting for approximately 70% of SCD cases worldwide. Illness related to SCA is an important public health problem as it is a serious chronic disease with limited possibility of cure and that causes suffering to its patients. With adult age and aging, cardiopulmonary changes are mainly observed. Given their high prevalence and the clinical impact caused to patients with SCA, this study compiled information about cardiopulmonary changes in patients with SCA.

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INTRODUCTION

Sickle cell anemia (SCA) is part of a group of hemoglobinopathies called sickle cell disease (SCD) in which individuals inherit hemoglobin variants derived from single-point mutations that result in morphological abnormalities in red blood cells. The SCA is the most common and severe form of the disease accounting for 70% of SCD cases in African ethnicity patients. Among the other forms of SCD, S β-thalassemia and heterozygous forms with hemoglobin C (HbC) and D (HbD) must be highlighted[1-3].

This hemoglobinopathy is characterized by an autosomal recessive mutation in the gene that produces HbA giving rise to HbS which forms red blood cells shaped like a crescent or sickle and makes blood oxygenation difficult causing various types of complications such as chronic hemolytic anemia, vaso-occlusive phenomena and consequent pain crises due to decreased blood perfusion. In addition, infarction and necrosis in various organs, such as bones, joints, spleen, lungs and kidneys may occur[4].

Illness related to SCD is an important public health problem worldwide as it has a great impact on morbidity and mortality in the affected population which in Brazil is estimated at 30000 patients with an annual increase of 3500 new cases. Furthermore, about 20% of children do not reach the first 5 years of life, especially when they do not have adequate medical care. It is a serious chronic disease with limited possibility of cure and that still causes significant suffering to its patients which requires special medical, genetic and psychosocial attention[5,6].

Advances in treatment and survival studies with patients with SCA demonstrates an improvement in life expectancy. A few years ago, this expectation was only 20 years which increased to an 85% chance of survival after 20 years and the implementation of neonatal diagnosis, education and comprehensive patient care programs. Although there is an increase in quality of life and longevity, clinical complications persist with adulthood and aging and others start to be observed. The chronic impact of hemolytic anemia and vaso-occlusive episodes lead to more evident progressive complications in target organs (lungs, heart, spleen, bones, brain, kidneys and skin). The development of cardiopulmonary manifestations associated with the disease include: Elevated pulmonary artery systolic pressure, pulmonary hypertension (PH), left ventricular diastolic heart disease, cardiac dysrhythmia and sudden death. In older patients, cardiopulmonary dysfunction is more intense and significantly contributes to morbidity and premature mortality[7,8].

Cardiomegaly is the main cardiac alteration seen in sickle cell patients. Myocardial dilatation and hypertrophy are other important manifestations. These changes result from hemodynamic dysfunction resulting from the reduced oxygen transport capacity imposing an increase in cardiac output (CO) which can reach up to 50% during rest in patients with SCA. This process occurs mainly due to a greater systolic volume because of the increase in preload: Product of cardiac dilation; and afterload: Due to lower peripheral vascular resistance (PVR). This hemodynamic overload also promotes the other clinical findings such as murmurs perceived on auscultation[9].

The overload in iron concentrations resulting from multiple blood transfusions is an additional factor in the pathogenesis of cardiac dysfunction. The main mechanism is related to the free iron ion that exceeds the body's capacity to store and neutralize this element through the chelation process. Excess free iron is gradually deposited in various organs or tissues such as the heart, contributing to organ dysfunction with dilation and hypertrophy, arrhythmia and heart failure[10]. The pathophysiological mechanisms described are characterized as adaptive actions against the aggressions produced by the disease and the persistence of the changes explains why it is uncommon for the physical examination of a patient with SCA to show no changes[9].

Pulmonary complications are the main causes of morbidity and mortality in patients with SCA in all age groups. It is estimated that 90% of these adult individuals have abnormal lung function. Chronic lung disease is likely a consequence of recurrent episodes of acute chest syndrome (ACS), infections, fat embolism and pulmonary infarction. It is believed that PH is one of the main causes of death in adult patients. However, only 10% of patients with SCA are monitored for early detection of PH. Its pathophysiological mechanism is complex and probably multifactorial[9,11]. Cardiopulmonary complications can develop independently and each one of them (cardiac or pulmonary) individually contributes to greater morbidity and mortality and the combination of both is an important aggravating factor in the worsening of the prognosis of these patients[11].

Given the high prevalence of cardiovascular and pulmonary abnormalities associated with SCA, the clinical impact caused in addition to compromising the quality of life of patients and the overcharge that it represents to the public health system, this study systematized and evaluated scientific publications on pulmonary complications and cardiovascular diseases in sickle cell patients from 1920 to 2020. This compilation aims to provide knowledge for health professionals and managers in order to draw attention to the importance of chronic diseases in SCA patients and in addition to providing elements that provide improvements in the management of useful resources that contribute to improve the quality and increase the life expectancy of these patients.

MATERIALS AND METHODS

This is a systematic review conducted in accordance with the PRISMA recommendation on cardiopulmonary alterations in patients with SCA. We also cite high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

Eligibility criteria

Types of studies: Articles that had as their object: Cardiac or pulmonary alterations in SCA published between 1990 and 2020 in English, Portuguese and Spanish were included. Also included were cross-sectional, descriptive, quantitative, cohort, meta-analysis, case-control and experimental studies.

Types of participants: Patients with SCA who have cardiopulmonary disorders.

Types of results: Scientific articles that include results of prevalence, relative risk, outcome or data analysis about cardiopulmonary complications in patients with SCA.

Information sources

The search and evaluation of scientific articles took place between June and September 2020 in the Scientific Electronic Library Online (SCIELO), United States National Library of Medicine (PUBMED) and Bibliteca Virtual de Saúde (BVS) databases.

Research

The search strategy in the PUBMED and VHL databases included the following keywords: "sickle cell anemia and cardiovascular complications", "sickle cell anemia and lung complications", "sickle cell anemia and cardiopulmonary anemia", "sickle cell anemia and cardiopulmonary", "sickle cell anemia and lung complications", "sickle cell anemia and cardiac complications", "sickle cell anemia and lung" and "sickle cell anemia and cardiac". For the SCIELO database, the terms used were: "sickle cell anemia and cardiopulmonary", "sickle cell anemia and lung changes" and "sickle cell anemia and lung".

Sample selection

Two authors of this study carried out the selection of articles independently (Silva Lopes J, Garcia Viana

Í). Subsequently, verification and exclusion of duplicates was performed with subsequent reading and selection of abstracts excluding those that did not directly address cardiopulmonary changes in patients with SCA. Finally, full reading of the articles was established including only those that met the eligibility criteria.

Data collection process

After reading the articles, the data of interest for this review were extracted using a collection instrument developed by the authors available in the supplementary material.

Data selection

The information extracted from the studies included: Year of publication, title, journal/magazine, article objective and content synthesis.

Risk of bias in each study: The main bias found in the cross-sectional studies presented here was the establishment of causality, an inherent characteristic of this type of study. Reduced sampling was reported in three articles. In case-control studies, a selection bias prevailed, especially in the selection of controls that were properly matched to the cases. In clinical trials, the most reported limitation was the difficulty in extrapolating the results to clinical management, due to the limited number of participants. The inability to apply "gold standard" tests was also mentioned in two articles. The sample size, the retrospective characteristic and the inability to use "gold standard" tests were the main limitations found in the cohort studies.

RESULTS

After applying the uni-terms, 6767 articles were found, distributed as follows: 3948 in PUBMED, 2797 in BVS and 22 in SCIELO. After applying the eligibility criteria, reading titles, excluding duplicates, reading abstracts and full texts, 27 studies that make up this review were selected (Figure 1). The main results of this study are summarized in Table 1.

Study characteristics

The decade from 2010 to 2020 concentrated the largest number of publications with a total of 21 (77.77%) studies, followed by the decade from 2000 to 2010, with 5 (18.51%) studies in this period. In the decade from 1990 to 2000 only one publication was found. In 2016, 5 studies (18.51%) were published, 2017, 4 (14.81%). In 2011 and 2015, 3 studies were published each year (11.11%). In 2008, 2012 and 2018, 2 articles.

The type of study most carried out in the period was cohort 10 (37.03%) followed by cross-sectional and case-control with 8 studies each (29.62%) and a multicenter study (3.70%). Regarding the language of publication, most were published in English 25 (92.59%), with one article in Spanish and another in Portuguese. As for the age range of the studies, 10 (37.03%) referred to adulthood, 9 (33.33%) referred to pediatric patients and 8 (29.62%) included both age groups.

DISCUSSION

In compiling the data from the 27 articles, it was possible to observe that the main cardiopulmonary changes described in sickle cell patients were: PH, acute thoracic syndrome (ATS), restrictive and obstructive respiratory dysfunctions, wheezing in children, increased tricuspid regurgitation velocity (TRV), enlargement of the left ventricle (LV) and left atrium (LA) and diastolic dysfunction with normal systolic function. It was also possible to observe that PH and ACS are among the most important causes of morbidity and mortality in patients with SCA.

Pulmonary complications in SCA

PH can be diagnosed through right cardiac catheterization, an invasive method that is the gold standard for diagnosis and non-invasively by measuring the TRV with diagnostic confirmation defined as a TRV ≥ 2.5 m/s. Caughey *et al*[12] demonstrated that most studied patients with suspected PH had elevated TRV and 59% had values > 3.0 m/s. A higher PH detection rate was observed by measuring TRV, highlighting a greater possibility of false-positive results with this method[11,13,14].

Dham *et al*[15] found that children with SCA had significantly higher TRV, systolic, diastolic and mean pulmonary artery pressures than controls. The highest frequency of pediatric patients with ACS and PH found was in the age group of 5-7 years. The high prevalence of PH among younger children is an uncommon finding as this complication is known to progress with age[16]. TRV values ≥ 2.5 m/s were shown to be correlated with a history of acute chest syndrome and previous transfusions. Elevated left atrial pressure and right ventricular stroke volume were predictors of TRV in a multivariate

Table 1 Comparative table of the studied articles

Ref.	Location	Type of study	*n*	Main results
Dham *et al* [15], 2009	Washington	Case control	364	Children with SCA have a mild increase in SCA, which correlates with increased cardiac output and left ventricular filling pressures
Cuervo *et al* [22], 2002	Cuba	Case control	53	Restrictive ventilatory dysfunction was observed in all patients with sickle cell anemia
Fitzhugh *et al*[19], 2010	North Carolina	Retrospective transversal	240	This study points out the main causes of death in patients with SCA. Among them are: Pulmonary emboli, stroke and multiple organ failure. In addition, it mentions the main pre-morbid conditions found: Pneumonia, congestive heart failure, myocardial infarction and arrhythmias
Parent *et al* [13], 2011	France	Transversal	398	Patients with confirmed pulmonary hypertension were older and had worse functional capacity than other patients
Damy *et al* [32], 2016	France	Transversal	1.780	TRV ≥ 2.5 m/s and left ventricular dysfunction predict mortality in patients with SCA
Arteta *et al* [27], 2014	Michigan	Cohort	146	It is common for children with sickle cell anemia to have abnormal lung function, most often of the obstructive type
Lobo *et al* [18], 2015	Rio de Janeiro	Prospective transversal	125	Patients over 32-years-old have mostly elevated LDH, severe anemia and creatinine clearance > 1, in addition to a poor prognosis, and may be at risk of developing pulmonary hypertension

SCA: Sickle cell anemia; TRV: Tricuspid regurgitation velocity; LDH: Lactate dehydrogenase.

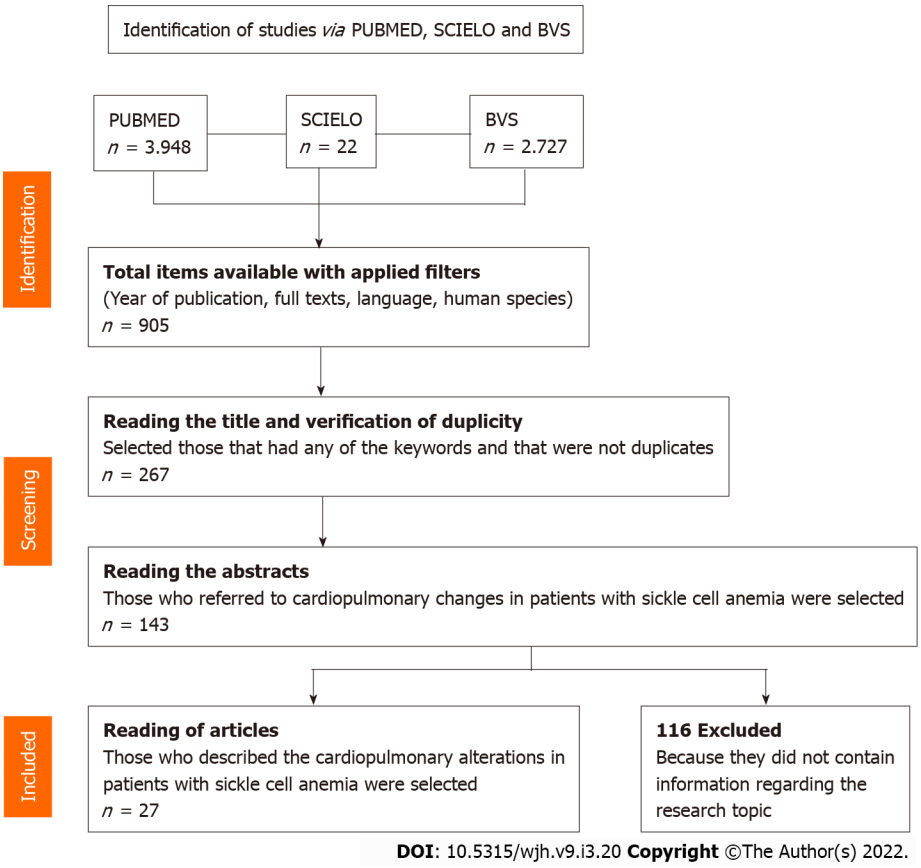

Figure 1 Flowchart of article selection for systematic review.

regression model. Higher TRV was also associated with increased left ventricular and atrium chambers and higher levels of B-type natriuretic peptide, lactate dehydrogenase (LDH), amino aspartate transferase (AST), erythropoietin, urea, creatinine and reticulocytes. Another clinical finding reported in the studies found was the presence of the second heart sound with greater intensity. This change was statistically associated with PH in children with ACS and individuals with this clinical finding demonstrated a 3.4 times greater chance of having PH[12,13,17-20].

However, PVR and Hb levels were indirectly related to the increase in TRV. For every 1.0 g/dL increase in Hb, TRV decreased by 13%. The data found suggested that most adult patients with ACS and suspected PH had normal PVR. Caughey *et al*[12] demonstrated that the mean PVR index was significantly higher in patients with suspected PH than in those without PH although they were still below the cutoff point for elevated PVR. Only 2 individuals with suspected PH (6%) with TRV values between 3.0 and 3.9 m/s, respectively, had a high PVR index[14,15].

The pathogenesis of PH in patients with SCD is complex. The compensatory state of high CO due to chronic anemia may contribute to increased pulmonary arterial pressure (PAP) in the presence of normal PVR. PH as a manifestation of left ventricular dilatation and eccentric hypertrophy may be significant in some patients. Hemolysis is also believed to play an important role leading to nitric oxide depletion, endothelin-1 release and platelet activation. Ultimately, they result in vasculopathy characterized by endothelial dysfunction, increased vascular tone, inflammation, hypercoagulability and vascular remodeling[12].

The strong and independent associations of TRV with the velocity-time integral of the right ventricular outflow tract and the left atrial pressure index support the importance of high CO in the pathogenesis of PH in this population. A possible role for hemolysis is suggested by the negative correlation of TRV with Hb and reticulocyte counts. Circulating erythropoietin concentrations reflect the degree of tissue hypoxia and the association of a higher level of erythropoietin with higher TRV may serve as a marker of the degree of tissue hypoxia which appears to be associated with the development of PH in other conditions[12,16,17].

ATS was reported in the study by Vichinsky *et al*[21] in which more than two-thirds of participants with SCA had a history of ACS with multiple episodes. The cause of ACS was established in 38% of the episodes with infections and pulmonary emboli (bone marrow, fatty or thrombotic) being the main ones reported. Of the 27 different pathogens identified, *Chlamydia* pneumoniae was the most prevalent followed by *Mycoplasma* pneumoniae.

Maioli *et al*[11] and Cuervo *et al*[22] showed that the pulmonary function test in patients with ACS can identify different elements related to the evolutionary stage of the disease, including restrictive ventilatory dysfunction, observed in patients with SCA, regardless of a previous history of SCA. However, a history of 2 or more episodes of AST makes this clinical manifestation the most important risk factor for chronic lung damage and consequently, characteristic ventilatory changes. MacLean *et al* [23] and Cuervo *et al*[22] also reported that obstructive pulmonary abnormalities occur first followed by the development of restrictive abnormalities which become more prominent with increasing age in children and adolescents with SCA. A history of asthma or wheezing, bronchopulmonary dysplasia, cystic fibrosis, bronchiolitis and a higher concentration of LDH were associated with obstructive pulmonary disease reflecting lower TFP values. It was also observed that low forced expiratory volume in 1 s (FEV_1%) was considered an independent predictor of early death in adults with SCA, with a decrease in FEV_1% being associated with an increase in the measurement of TRV[23,24].

Throughout life, patients with SCA have the lung parenchyma subject to episodes of ischemia during vaso-occlusion crises. These events sometimes lead to necrosis and subsequent regeneration with formation of fibrotic tissue. These pathophysiological mechanisms can occur during ACS or in the course of a vaso-occlusive chest crisis so that with advancing age, the lung parenchyma starts to present more fibrotic tissue contributing to the onset of the restrictive change which justifies the increase in the percentage of restrictive disorders from the age of 25 onwards. An association between restrictive changes and increased left ventricular size was also observed. LV dilation can reduce lung volume due to pulmonary congestion and the direct effect of heart compression on the lung parenchyma. In obstructive changes, they reported that increased capillary blood volume and hemolysis may contribute to increased airway obstruction in children with SCA[11,23-28].

Other pulmonary alterations associated with SCA have been described: Mosaic attenuation pattern on computed tomography (CT) associated with increased TRV, decreased hemoglobin levels and reduced respiratory muscle strength in a ground-glass pattern. Furthermore, it has been reported that children with sickle cell have more frequent wheezing compared to children without SCA and that leukocytosis is considered a risk factor for early decline in pediatric lung volumes[11,29,30]. Several mechanisms may be involved in the decrease in respiratory muscle strength in these patients: Shallow breathing due to chest pain, vaso-occlusion that affects muscle performance and chest cavity deformities resulting from successive bone infarctions. The results of the study by Maioli *et al*[11] suggested that the partial collapse of airway spaces after inspiration, due to respiratory muscle weakness, may explain the matte pattern in the CT of these patients. The association between elevated TRV and the appearance of a mosaic attenuation pattern on CT is indicative of occlusive vascular disease and small airway obstructive disease.

The finding of wheezing on pulmonary auscultation also supports the appearance of obstructive disease. However, the mechanisms by which leukocytes can affect lung volumes are not clear. Leukocytes are able to adhere to blood vessel walls and obstruct the lumen. They also stimulate the vascular endothelium resulting in a cascade of events that lead to tissue damage and an inflammatory reaction that further favors the phenomenon of vaso-occlusion[29,30].

Cardiac complications in SCA

The most reported cardiac alteration indicated is an enlargement of the LV and atrium and prolongation of the corrected QT (QTc) interval on the electrocardiogram. Patients with SCA also had diastolic dysfunction with increasing age (with preservation of systolic function) and, in some cases, systolic dysfunction[31,32]. The pattern of diastolic dysfunction, left atrial dilation and normal systolic function observed in these patients is consistent with an aspect of restrictive cardiomyopathy. Elevated TRV is correlated with increased PAP, being the result of pulmonary arterial endothelial dysfunction due to intravascular hemolysis. However, restrictive physiology also increases PAP and TRV secondary to increased LA pressure[31,33].

Diastolic dysfunction may also result from a combination of myocardial fibrosis, microvascular occlusions by sickle cells, ischemic events, cardiomyocyte loss and oxidative stress. Niss *et al*[33] reported that individuals with advanced fibrosis had concomitant diastolic dysfunction. These progressive myocardial injuries promote dilatation and increased pressure in the LA and a slight increase in retrograde pulmonary venous pressure[33,34]. The increase in LV is mainly due to hyperdynamic circulation related to anemia. In addition, abnormal loading conditions associated with anemia also lead to its dilation and consequent increase in stroke volume. Other factors, including iron overload, immunogenic factors, damage to the microcirculation from vaso-occlusive crisis and associated valvular disease may contribute to the remodeling process and cardiac dysfunction[31,33,34].

Indik *et al*[32] reported that prolongation of the QTc interval on the electrocardiogram was present in 39% of men and 27% of women with SCA and associated with higher values of TRV. A QTc interval greater than 450 ms in men and 470 ms in women was associated with a higher risk of death. Thus, the presence of multiple vaso-occlusive episodes throughout life may also contribute to QTc interval prolongation, coronary microvascular dysfunction and increase the risk of sudden death in SCD.

The studies compiled herein showed an important frequency of pulmonary and cardiac impairment in patients with SCA. The treatments now available have contributed to increase the life expectancy of patients. The increase in the average age of patients may imply an increase in the prevalence of cardiopulmonary alterations, in addition to other comorbidities associated with the disease. This scenario suggests the need to improve specialized and early care for these patients, especially with a view to early diagnosis of dysfunctions and monitoring of cardiopulmonary function from childhood, aiming to promote a decrease in the worsening of cases of pulmonary and cardiac dysfunction, contributing to improvement of the cardiopulmonary function of these patients and above all, allow guarantees of a better quality and expansion of life expectancy for this population.

CONCLUSION

The findings presented here suggest that cardiopulmonary alterations have an important negative clinical repercussion in patients with SCA. These changes are the result of multiple etiologies: Inflammatory, restrictive, obstructive, remodeling and vaso-occlusive. Among the changes, it is worth highlighting the high prevalence of PH, ventricular hypertrophy and diastolic dysfunction. The increased survival of patients with SCA highlights the need to develop strategies aimed at improving the quality of life of these patients. These interventions involve improving the early diagnosis of cardiopulmonary changes with specific tests and family guidance in the face of the first signs of these complications (wheezing, dyspnea and chest pain). Public health strategies for the diagnosis and monitoring of cardiopulmonary dysfunction in patients with SCA must necessarily offer specialized medical care with a specialist and complementary diagnostic tests that are sufficient for the conclusive diagnosis and treatment of clinical complications secondary to cardiopulmonary alterations.

Early diagnosis, follow-up and specialized treatment may contribute to reducing the episodes of hospital admissions due to complications which may impact on cost reduction to the health system since it is a disease that can generate long periods of hospital admissions in situations of worsening of the condition, in addition to the human impact caused. Basic health care through more frequent follow-up at basic health units, blood centers and other secondary care units and immediate seeking of medical assistance in possibly serious situations such as episodes of pain crises can determine, in the long term, less need for hospital admission.

ARTICLE HIGHLIGHTS

Research background

Sickle cell anemia (SCA) is part of a group of hemoglobinopathies called sickle cell disease (SCD) in which individuals inherit hemoglobin variants derived from single-point mutations that result in morphological abnormalities in red blood cells.

Research motivation

Illness related to SCD is an important public health problem worldwide as it has a great impact on morbidity and mortality in the affected population which in Brazil is estimated at 30000 patients with an annual increase of 3500 new cases. Furthermore, about 20% of children do not reach the first 5 years of life, especially when they do not have adequate medical care.

Research objectives

This study aimed to systematically compile information about cardiopulmonary changes in patients with SCA.

Research methods

A systematic literature review was performed based on the PRISMA recommendation including scientific articles indexed in the Scientific Electronic Library Online databases, United States National Library of Medicine and Biblioteca Virtual de Saúde. The search period was delimited between 1990 and 2020 and selected in Portuguese, English and Spanish. Three sets of descriptors were used for each database including only research carried out with human beings. After reading the articles, those useful for this review were extracted using a collection instrument designed for this purpose. The final selection included 27 studies.

Research results

The year with the highest number of publications was 2016 with 5 studies (18.51%), followed by 2017 with 4 (14.81%). The type of study most carried out in the period was cohort 10 (37.03%) followed by cross-sectional and case-control with 8 studies in each (29.62%). Regarding the language of publication, the distribution was as follows: 25 (92.59%) in English, 1 (3.70%) in Spanish and 1 (3.70%) in Portuguese.

Research conclusions

The findings of the present study suggest that cardiopulmonary alterations represent a serious clinical repercussion of SCA. Of the analyzed studies, the high occurrence of pulmonary hypertension, ventricular hypertrophy and diastolic dysfunction stands out as the main cardiopulmonary complications.

Research perspectives

In view of the increased survival in SCA, there is a need for surveillance and the development of strategies aimed at preserving the cardiopulmonary function and, consequently, improving the quality of life of these patients.

FOOTNOTES

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