A Rare Case of Pulmonary Neuroendocrine Carcinoma in Transfusion-dependent Thalassemia Patient: Clinical Presentation, Management, and Implications

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ABSTRACT

Transfusion-dependent thalassemia (TDT) is often accompanied by complications related to iron overload and the development of malignant solid tumors or hematological malignancies. The occurrence of Neuroendocrine carcinoma, specifically in the respiratory tract, is very rare, with a prevalence of approximately 25%. Therefore, this study presented a case of a 42-year-old male with a beta-thalassemia major at 28 years, complaining of shortness of breath. This case was reported due to its rarity in providing information about solid tumors in thalassemia patients. The physical examination revealed several symptoms, including tachycardia, tachypnea, anemia, icteric sclera, elevated jugular venous pressure, coarse wet Ronchi in the medial to basal areas of both lungs, hepatomegaly, and splenomegaly (Schuffner 4). The patient regularly received blood transfusions and iron chelation therapy. A thoracic CT scan showed a lung mass and a biopsy of the mass revealed Pulmonary Neuroendocrine Carcinoma with high-grade proliferation and, large cell type. The patient also passed through cisplatin-etoposide chemotherapy for 6 cycles every 21 days. There is almost no data on pulmonary neuroendocrine carcinoma in thalassemia patients, so it is hoped that this case report can provide information about malignant solid tumors that can occur in thalassemia patients.

Keywords: *Malignant solid tumor, Neuroendocrine Carcinoma, Thalassemia.*

INTRODUCTION

Thalassemia is a commonly encountered hemoglobinopathy, with approximately 40.000 new cases reported annually and over 80 million cases of thalassemia carriers. Among patients with beta-thalassemia (B-thalassemia), there are two types distinguished based on clinical presentation, namely transfusion-dependent thalassemia (TDT) major and non-transfusion-dependent thalassemia (NTDT) intermedia (TI).[1] B-thalassemia major is a severe form of B-thalassemia resulting from mutations in the beta-globin gene, leading to reduced (B+) or non-reduced (B0) hemoglobin A. Therefore, unbound alpha globin chains accumulate in erythroid precursors in the bone marrow and mature red blood cells, causing ineffective erythropoiesis and peripheral hemolysis. A previous estimation

has shown that 1.5% of the world population are carriers of B-thalassemia.[2]

The prevalence of neuroendocrine carcinoma (NEC) in solid tumors is low. Neuroendocrine neoplasms (NENS) account for approximately 0.5-2% of all malignancies and are heterogeneous groups of tumors that form neuroendocrine cells throughout the body. Most NENs occur in the gastrointestinal tract (62-67%) and the lung (22-27%). NECs are subtypes of NENs that are poorly differentiated and more aggressive, with a higher prevalence in the bone marrow (12-20%). The most common malignant solid tumors in thalassemia are breast, renal, and lung cancer.[3] The prevalence of NEC in hematological malignancies is extremely rare. Most reported cases are NECs with bone marrow invasion, but there are no studies that can specifically state the prevalence of NECs in hematological malignancies. The most common hematologic malignancies that often occur in thalassemia are leukemia and lymphoma.[4,5]

The exact mechanisms underlying the development of both malignant solid tumors and hematological malignancies in thalassemia patients are not yet fully understood, however, several hypotheses have played a role in this process. One hypothesis suggests that iron overload resulting from blood transfusions is a risk factor for cancer occurrence in both TDT and NTDT patients.[5]

CASE ILLUSTRATION

A 41-year-old male presented with shortness of breath accompanied by lower back pain, which had been occurring for approximately 3 months and worsened in the 4 days before admission. The patient reported a cough with whitish sputum, the onset of shortness of breath, weight loss, an enlarged abdomen, and yellowing of the eyes over the past year. Furthermore, the patient was diagnosed with transfusion-dependent thalassemia (TDT) in 2009 and regularly required blood transfusions, approximately 1-2 units of packed red cells per month. The sibling also suffered from thalassemia and received regular transfusions, but there was no history of cancer in the family.

General condition: The patient appeared severely ill with conscious mental status. Body weight 48 cm, height 158 cm, body surface area (BSA) 1.46. Vital signs showed tachypnea (28 times per minute), tachycardia (110 beats per minute), blood pressure of 110/60 mmHg, temperature of 36.7^{0}C, SpO2 of 88% on room air, and 95% with a simple mask at 8 liters per minute. Physical examination: The patient appeared pale (+), and rodent facies (+). Heart: Increased jugular venous pressure (JVP) of 5+3 cm H2O, no visible or palpable cardiac apex at the sixth intercostal space (ICS VI), 2 cm from the midclavicular line on the left. Lungs: Difficult evaluation of vocal fremitus, coarse wet rhonchi in both lungs' medial and basal parts. Abdomen: Liver span of 10 cm, splenomegaly schuffner 4, shifting dullness (+), and dullness on percussion (+). Extremities: bilateral leg edema with overall yellowish skin appearance.

Laboratory examination revealed normochromic normocytic anemia (7.2 gr/dl, MCV/MCH 61.9 fl/18.4 fl), RET HE 17.3 (32.1-38.8), ALT 79 U/L (N: 15-37 U/L); AST 81 U/L (N: 0-55 U/L), Hb electrophoresis HbA 4.9 (N: 97-98.5), HbA2 5.5 (N: 2.5-3.0), HbF 30.7 (N: <0.4), Conclusion: HbE Beta+ Thalassemia.

Chest X-ray posteroanterior examination revealed a dense, well-defined opacity with irregular edges and calcification, suggestive of a mediastinal mass. Nodular opacities were observed in the bilateral mid-lung fields, suspicious for intrapulmonary metastases, and right-sided pneumonia was also suspected.

Abdominal ultrasonography revealed hepatomegaly with dilated hepatic vein and inferior vena cava, accompanied by splenomegaly and ascites, supporting the diagnosis of congestive hepatopathy. Sludge in the gallbladder, bilateral pleural effusion, and no visible enlargement of the paraaortic/parailiac lymph nodes were observed. Currently, there were no abnormalities detected in the ultrasound examination of the pancreas, bilateral kidneys, and urinary bladder.

The abdominal CT scan revealed hepatosplenomegaly and ascites with bilateral pleural effusion. A solid, heterogeneous mass was visualized in the lower anterolateral

thoracic paravertebral region, appearing oval and elongated, pushing the heart anteriorly. The measured size of the right visualized mass was 7.5x7.3x8 cm, and the left was 4.5x4.0x8.5 cm, which extended into the intrapulmonary. The mass partially destructed the posterior ribs at the level of T9-10. Consolidation with air bronchograms and posterobasal pleural effusion were observed and cardiomegaly was also present. Additionally, a round, elongated mass was observed in the anterior sacrum, destructing the sacral bone from S1 to the sacrococcygeal region. The measured size of the mass was 8.3x7.5x12 cm, indicating bone metastasis sarcoma.

Thoracic CT scan showed a lobulated mass in the right and left paravertebral regions with well-defined borders, ranging from T4-T5 to T12-L1, predominantly visualized as a large inferior mass at T8-T9 measuring 7.8x7.5 cm on the right and 5.6 x 5.9 cm on the left. The mass appeared heterogeneous after contrast application, caused the destruction of the ribs, and adhered to the posterolateral wall of the pleural cavity. The mass also extended anteriorly, with thickening of the intercostal soft tissue and anterior-posterior destruction of the ribs from T4 inferior. The liver metastasis was not detected but mild cardiomegaly was present and the differential diagnosis included large cell lymphoma or metastasis.

CT pulmonary angiogram showed (**Figure 1**) an approximately 1.11 increased ratio between the main pulmonary artery and ascending aorta, suggesting pulmonary hypertension type V. There was cardiomegaly with dilatation of the right atrium, right ventricle, and concentric hypertrophy of the left ventricle. Lytic lesions with coarse trabeculae were also observed in the corpus vertebral rib, sternum, calculi, scapulae, and proximal bilateral humerus, suggesting thalassemia bone disease with associated extramedullary hematopoiesis at thoracic paravertebral region and anterior aspect of the bilateral ribs. Ground-glass opacities were present in all segments of both lungs, accompanied by patchy consolidation in the medial and lateral segment of the right middle lobe, as well as fibrosis in the medial segment of the right middle lobe and posterior basal segment of the inferior lobe of the right lung. The anteromedial segment of the inferior lobe showed

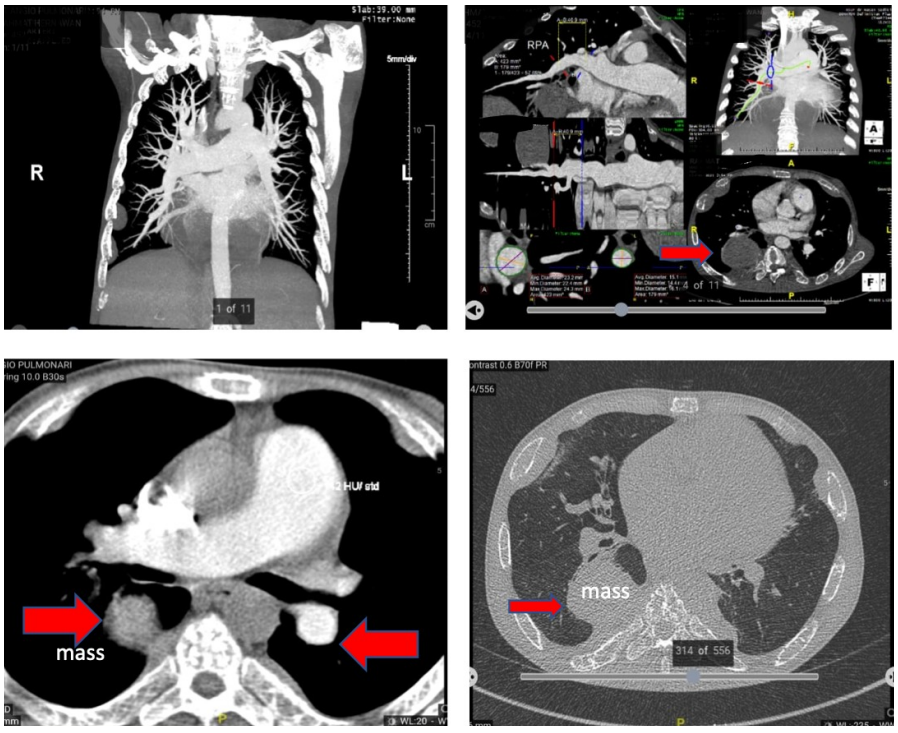

Figure 1. The red arrow on CT Angiography demonstrates the presence of an intrapulmonary mass in the thoracic paravertebral region. The mass appears to be attached to the posterolateral wall of the pleural cavity and extends anteriorly with the thickening of the intercostal soft tissue.

evidence of a chronic inflammatory process with secondary infection.

Bronchoscopy showed constrictive stenosis suspected to be malignant. Biopsy results revealed non-Hodgkin lymphoma with a differential diagnosis of neuroendocrine carcinoma of the right lung. Therefore, it was recommended to perform immunohistochemical examinations for CD3, CD20, Ki-67, NSE, synaptophysin, and chromogranin to confirm the diagnosis.

The core biopsy showed macroscopic findings of fragmented tissue weighing 0.2 grams, with a whitish-brown color. Microscopic examination revealed a tumor mass composed of hyperplastic oval-shaped cells that were densely packed, and characterized by pleomorphic nuclei. Mitosis was observed and the tumor cells appeared to infiltrate the surrounding stroma. The differential diagnosis concluded non-Hodgkin malignant lymphoma with the possibility of neuroendocrine carcinoma. Therefore, immunohistochemical examination (hematoxylin and eosin stain, original magnification, x400) for CD3, CD20, Ki-67, NSE, synaptophysin, and chromogranin was recommended to confirm the diagnosis. The results showed negativity for CD20, CD3, synaptophysin, and NSE, as well as positivity for Chromogranin and Ki-67, with a proliferation rate of over 50% indicating high proliferation **(Figure 2).**

The echocardiography showed dilated RA, RV, and D-shaped LV, with normal LV systolic function, and LVEF of 64.6% (Simpson's). There was global normokinesis at rest, diastolic dysfunction grade II, moderate TR, high probability of PH, normal RV contractility, IAS gap (+), unclear visibility of shunt, and mild localized pericardial effusion (0.5-0.7 cm) at the posterior wall. Furthermore, there was no sign of cardiac tamponade, with maximum and minimum IVC of 3 cm and 1.6 cm, respectively.

The therapies administered during the treatment included fluid therapy, enoxaparin injection, furosemide injection, lovenox injection,

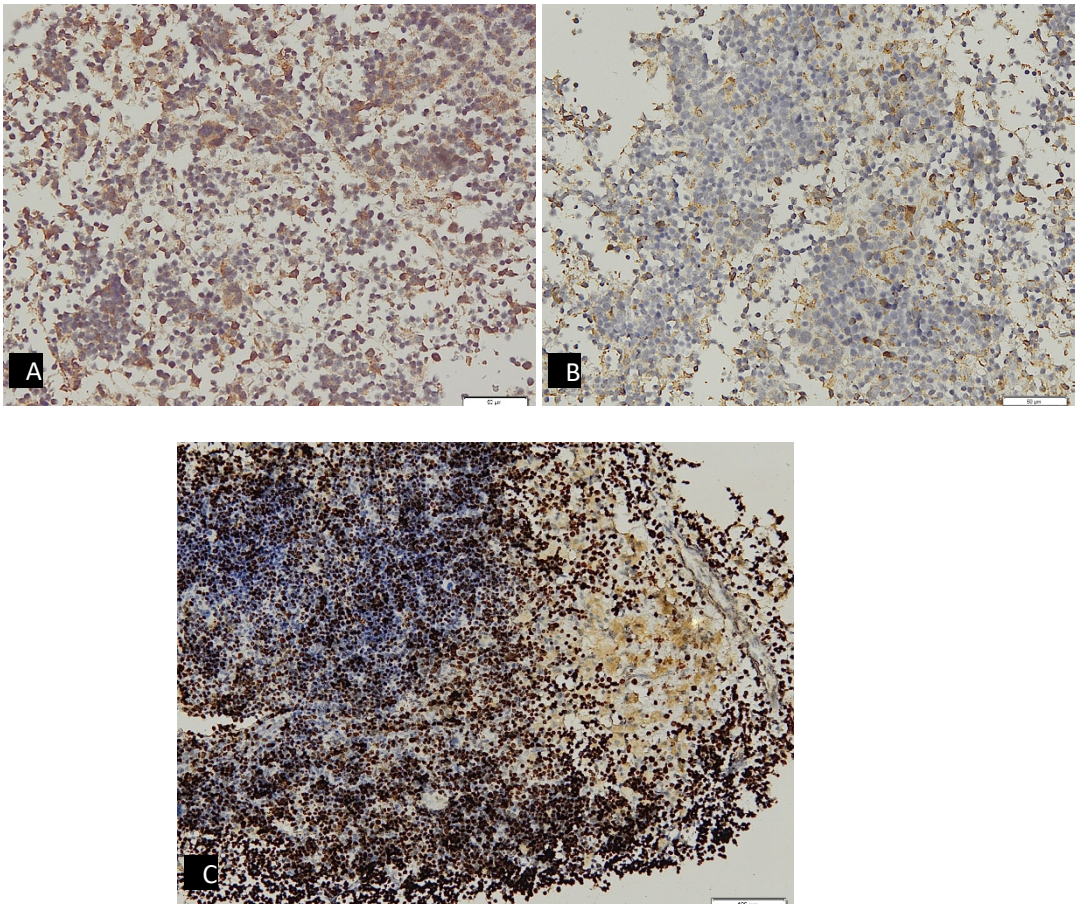

Figure 2. Immunohistochemical showed (hematoxylin and eosin stain, original magnification,x400): A. Chromogranin positive, B. Synaptophysin negative, C. Ki 67 > 50% highproliferation.

levofloxacin infusion, methylprednisolone injection, omeprazole injection, nebulization with meprovent and pulmicort, and cefepime injection to manage shortness of breath caused by pneumonia infection and pulmonary hypertension in the patient.

During the visit to the medical hematology-oncology outpatient clinic, further investigation was conducted on the lung mass, based on the results of chest X-ray, bronchoscopy, contrast-enhanced thoracic CT scan, thoracic CT angiography, abdominal ultrasound, anatomical pathology, and immunohistochemistry. The diagnosis obtained was Pulmonary Neuroendocrine Carcinoma, a high-grade proliferation type large cell, with pulmonary hypertension.

Based on the NCCN guidelines version 2.2022, the treatment option given to the patient was Cisplatin-Etoposide, administered for 6 cycles every 21 days. The dose we are giving for this patient is cisplatin 25 mg/m^2 (36.5 mg) and etoposide 50 mg/m^2 (adjusting dose based on increase of AST (76 mg).

DISCUSSION

This study reported a rare case of Pulmonary Neuroendocrine Carcinoma with high-grade proliferation of large cells and pulmonary hypertension in a patient with TDT. The diagnosis of the patient was established based on the history, physical examination, and supporting investigations including chest X-ray, CT-scan thorax with contrast, CT angiopulmonary, anatomical pathology, and immunohistochemical examination.

The incidence of pulmonary neuroendocrine carcinoma in patients with thalassemia has not been widely reported. Previous studies have investigated neuroendocrine carcinoma cases, which are commonly found in the pancreas. Although the incidence of neuroendocrine tumors is very rare, the number of cases is increasing each year. Pulmonary neuroendocrine tumors (PNETs) consist of a heterogeneous group of tumors, including typical carcinoid (TC), atypical carcinoid, large-cell neuroendocrine carcinoma, and small-cell carcinoma, which exhibit the same morphological, molecular, and immunohistochemical characteristics.[6]

The grading of PNETs is based on mitotic activity, presence of necrosis, and Ki 67 proliferation index. According to the survival analysis, large-cell and small-cell neuroendocrine carcinoma have poor survival rates.[4]

Neuroendocrine carcinoma is classified as a poorly differentiated neuroendocrine neoplasm with a high proliferation rate, determined by Ki-67 examination >20% (WHO G3), typically Ki-67 >50%. An immunohistochemical examination is crucial in establishing the diagnosis of neuroendocrine carcinoma, with two recommended neuroendocrine markers, namely synaptophysin and chromogranin (CgA). In this case report, the immunohistochemical findings supported the diagnosis of neuroendocrine carcinoma, as the chromogranin test yielded positive results, synaptophysin was negative, and Ki-67 was >50%, indicating high proliferation.[7]

The occurrence of NETs in the respiratory tract accounts for approximately 25.3% and 67.5% in the digestive tract. NETs are rarely found in children and are more commonly observed in individuals over 50 years of age. The incidence of NETs cases is twice as high in males compared to females. In this case report, a 42-year-old male patient was presented with complaints of shortness of breath.[8]

According to the 2022 NCCN guideline, the evaluation principles for NETs in the bronchopulmonary system involved performing a CT scan thorac with contrast, multiphasic abdominal CT scan, or MRI, considering SSTR-PET/CT or SSTR PET/MRI imaging. Brain MRI, bronchoscopy, and testing for hypercortisolism and carcinoid syndrome should also be conducted based on clinical indication. Laboratory tests must be tailored to clinical indications, genetic counseling, and examination for inherited genetic syndromes.[9] In this study, the patient was diagnosed with Pulmonary Neuroendocrine Carcinoma high-grade proliferation, type large cell. According to the NCCN guidelines, the recommended treatment for clinically progressive tumors or symptomatic disease was chemotherapy using a cisplatin and etoposide regimen. The administration of cisplatin and etoposide chemotherapy was based on the

availability of treatment in the hospital and coverage by insurance. Cisplatin and etoposide chemotherapy were given for a total of 6 cycles every 21 days. The dose we are giving for this patient is cisplatin 25 mg/m^2 (36.5 mg) and etoposide 50 mg/m^2 (adjusting dose based on increased AST) (76 mg).[9]

In this case, the patient was diagnosed with B-thalassemia major at 28 years and received regular transfusions as well as iron chelation therapy. With the effective administration of iron chelation therapy and safer transfusion practices in developing thalassemia patients, the survival rate was significantly improved. However, along with advancing age, there were new complications and several morbidities continued to emerge with higher incidence rates, including malignant solid tumors in the field of oncology.[10]

Factors that can contribute to the occurrence of malignancies in thalassemia patients include oxidative damage resulting from iron accumulation, immunological abnormalities, viral infections, drug use such as hydroxyurea, and bone marrow stimulation due to chronic anemia. These factors increase the risk of cancer in thalassemia patients compared to the general population.[7] However, investigations regarding the relationship between thalassemia and malignancies are still limited, with the majority of epidemiological data derived from national multicenter studies and some case reports.[11]

The study conducted by Mohammed et al. indicated that the types of malignant solid tumors collected from various literature sources in patients with thalassemia who received regular transfusions or had TDT included hepatocellular carcinoma, thyroid cancer, renal cell carcinoma, breast cancer, and unspecified carcinoma.[5]

The exact mechanisms underlying the development of both malignant solid tumors and hematological malignancies in thalassemia patients are not yet fully understood, however, several hypotheses have played a significant role in this process. One hypothesis suggests that iron overload resulting from blood transfusions is a risk factor for cancer development in both TDT and NTDT patients. Routine blood transfusion leads to iron accumulation, hepcidin suppression due to anemia, and ineffective erythropoiesis, resulting in increased iron absorption in the intestines and excessive iron accumulation within cells, which causes redox reactions and toxicity. When cellular iron levels exceed the capacity of ferritin synthesis within cells, cell death, and organ damage occur due to exposure to reactive oxygen species (ROS) and resulting mutation **(Figure 3).**[5, 12]

Iron excess due to long-term transfusions can disrupt the balance of immune system regulation, leading to reduced immune responses mediated by antibodies and impaired phagocytic capacity of monocytes and macrophages stimulated by mitogens. This can also increase the risk of infection processes. Iron overload can also lead to the modulation of T-cell ratios, specifically a decrease in the CD4/CD8 ratio, and the modulation of cytokine activity, which disrupts the function of cytotoxic T cells. The cytotoxic T cells play a crucial role in combating viruses and malignant cells, thereby contributing to the development of cancer.[13,14]

Most of the data in the literature focus on the anti-tumor effects derived from iron-chelating agents that can induce apoptosis in cancer cells. Currently, numerous studies are being conducted to investigate the molecular mechanisms underlying the effects of iron chelators in cancer therapy.[15]

Deferoxamine has been shown to enhance the migration and invasion of cancer cells in vitro, specifically in cancer cell lines, through a consistent process of the epithelial-mesenchymal transition.[16] Moreover, deferoxamine can increase the metastatic potential of cancer cells, as observed in the breast cancer cell line MDA-MB-231, through the hypoxia-inducible factor-1α (HIF-1α) pathway. This involves the generation of ROS and the activation of extracellular signal-regulated kinase (ERK).[17]

Blood transfusions pose a high risk of transmitting an oncogenic virus, which contributes to the development of hematological malignancies. For example, the hepatitis C virus can progress to hepatocellular carcinoma. Meanwhile, cytomegalovirus and Epstein-Barr virus have been identified in TDT patients, which are associated with Hodgkin's lymphoma or non-Hodgkin's lymphoma. The human

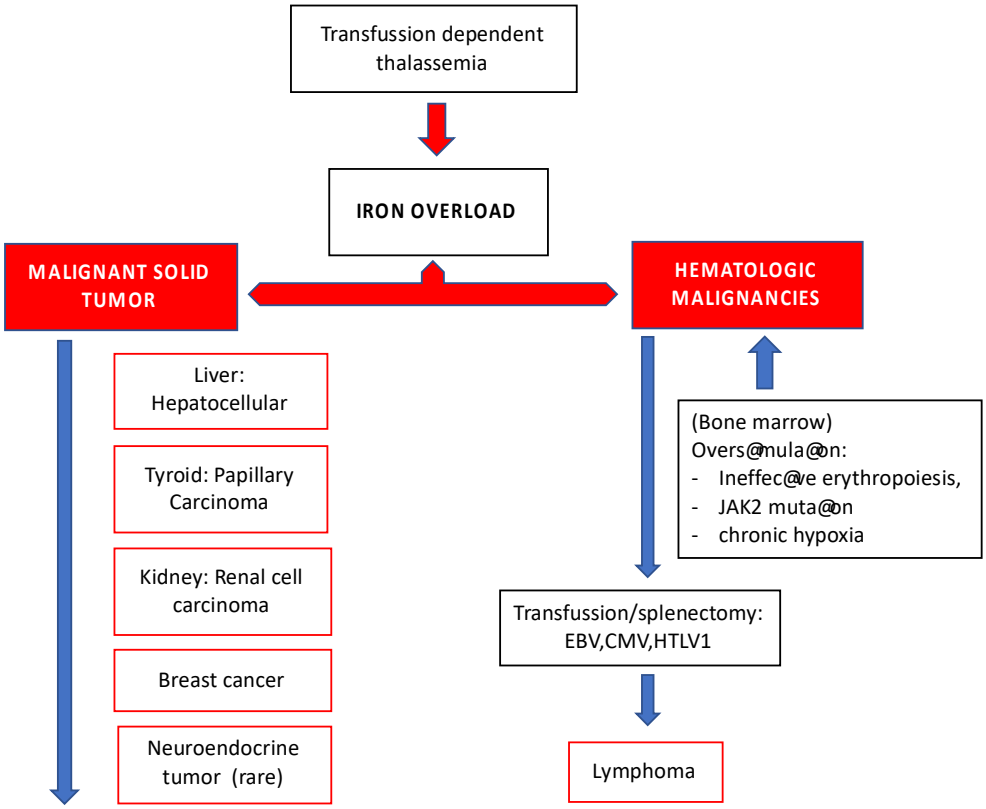

Figure 3. The hypothesis for the formation of malignant solid tumors and hematological malignancies in thalassemia patients

T-lymphotropic virus type-1 (HTLV-1) has been found in the thalassemia patients' population and is associated with T-cell leukemia or lymphoma.[18,19]

In patients with NTDT, the induction process of hematological malignancy is caused by ineffective erythropoiesis and the occurrence of hypoxia, leading to increased stimulation in the bone marrow. This high stimulation promotes erythroid progenitor cell proliferation and expansion of multiple cell lines, thereby triggering genetic aberrations that play a role in the development of hematological malignancies.[18,19]

CONCLUSION

This study presented a case of a 42-year-old male patient with B-thalassemia major who developed Pulmonary Neuroendocrine Carcinoma. The results showed that the thalassemia patients population appeared to have a higher tendency to be at risk for cancer. The incidence of solid and hematological malignancies has significantly increased due to the aging population with thalassemia. Several potential risk factors also contributed to the predisposition to malignancy among this population. Therefore, screening examinations for various types of malignancies should be conducted for all thalassemia patients based on the type of cancer and the presence of alarming symptoms for early diagnosis and treatment.

CONFLICT OF INTEREST

The author(s) declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

LS, AO, and DP participated in manuscript ideation. LS wrote the draft. AO and DP reviewed the draft and finally approved it.

ETHICAL APPROVAL AND INFORMED CONSENT

ethical approval is not required for case reports at our institution. Written informed consent was obtained from the patient for clinical and education purposes as per standard practice at our institution.

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