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A challenging convergence of conditions in a patient with thalassemia major presenting with thymoma and lymphangioleiomyomatosis: a case report

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Abstract

Background β-Thalassemia major is a complex, multisystemic condition. Effective transfusion programs, optimal iron chelation therapy, and progresses in magnetic resonance imaging have significantly improved patient survival. Despite these advancements, the fundamental pathophysiology remains unaltered, leading to an increase in comorbidities and cancer diagnoses with advancing age. We report a unique case of coincidentally discovered thymoma and lymphangioleiomyomatosis in a patient with β-thalassemia major.

Case presentation A 56-year-old Italian female patient with β-thalassemia major underwent magnetic resonance imaging to quantify myocardial, hepatic, and pancreatic iron deposition. Her medical history included transfusion-dependent β-thalassemia, splenectomy, and cholecystectomy. At the time of magnetic resonance imaging, she had no significant endocrine, cardiac, or hepatic complications and was on deferasirox, vitamin D, and luspatercept. Magnetic resonance imaging revealed a lobulated mass in the prevascular mediastinum, which showed mild radiotracer uptake on positron emission tomography. Chest computed tomography revealed multiple thin-walled cysts in the lungs, indicating lymphangioleiomyomatosis. Following multidisciplinary evaluation, the patient underwent thoracoscopic thymectomy and lung wedge resection. Histopathology confirmed type B2 thymoma and pulmonary lymphangioleiomyomatosis. Post-surgery, the patient was recommended for adjuvant radiation therapy and sirolimus treatment.

Conclusion This is the first reported case of the coincidental discovery of thymoma and lymphangioleiomyomatosis in a patient with β-thalassemia major. This case emphasizes the importance of thorough radiologic evaluations in patients with β-thalassemia to detect potential neoplastic conditions early. Enhanced awareness among clinicians and radiologists is crucial for the timely diagnosis and management of these patients.

Keywords Thalassemia, Hemoglobinopathies, Oncology, Interstitial lung disease, Lymphangioleiomyomatosis, Thymoma

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Background

β-thalassemia major is a complex and multisystemic condition in which the implementation of effective transfusion programs, together with the utilization of optimal iron chelation therapy, aided by advancements in magnetic resonance imaging (MRI), has resulted in a dramatic improvement in the survival of patients [1–3]. Nevertheless, these advancements were unable to completely eradicate the fundamental pathophysiology. Consequently, with advancing age, a greater number of comorbidities began to appear at a higher rate, with a subsequent diagnosis of more cancers, some of which may go undetected [4, 5].

We present the unique association of thymoma and lymphangioleiomyomatosis (LAM), both incidentally discovered, in a patient with β-thalassemia major.

Case presentation

A 56-year-old Italian female patient with β-thalassemia major presented to the radiology department to undergo MRI to quantify myocardial, hepatic, and pancreatic iron deposition. The clinical history of the patient included a transfusion-dependent β-thalassemia condition (genotype HBB:c.118C > T/ HBB:c.93-21G > A), diagnosed at the age of 7 years, despite the fact that the first transfusion was carried out at 2 years. As a consequence of β-thalassemia, the patient underwent splenectomy and cholecystectomy.

At the moment of MRI, she had a negative HCV-RNA (Hepatitis C virus-Ribonucleic acid) test, no osteoporosis or other endocrine, cardiac, or hepatic complications, and good iron levels. The patient's therapy included iron chelation with deferasirox, vitamin D, and luspatercept, an erythropoiesis modulator started 2 years before the MRI examination (good response, with an increase of about 35% of transfusion interval duration). Transfusion therapy included two units of concentrated and filtered red blood cells every 25 days with pre-transfusion hemoglobin values of 10–10.5 g/dl.

On MRI, a solid mass with lobulated and regular contours was incidentally identified within the prevascular compartment of the mediastinum (Fig. 1).

The lesion was mildly hyperintense on T2-weighted images (T2-wi) and isointense on T1-wi. The mediastinal mass in question was discernible in a prior MRI examination conducted for the same purpose in 2020 before starting luspatercept therapy, albeit with a marginal enlargement.

There were no other apparent abnormalities observed in the remaining mediastinal compartments. No pleural or pericardial effusions were present.

The neurological examination was unremarkable, and in the preceding months, the patient exhibited no symptoms of mediastinal syndrome associated with compression of the adjacent neurovascular structures. Moreover, she did not exhibit any fever or experience any weight loss.

For further evaluation, the patient underwent 18F-deoxyglucose (18FDG) positron emission tomography (PET)-computed tomography (CT) and chest CT with contrast media. On PET-CT, the mediastinal mass showed only mild FDG uptake (SUVmax = 4.3); no other sites of abnormal radiotracer uptake were reported in the neck, chest, abdomen, and skeleton. On CT images, the lesion presented regular margins, solid density, and mild contrast enhancement. The adjacent structures did not exhibit any signs of invasion, and lymphadenopathies or extra-thoracic disease were not present (Fig. 2). Such radiological features, the indolent behaviour over time, the absence of systemic symptoms, and the lack of avid FDG uptake on PET-CT scan made the diagnosis of thymoma probable.

However, on lung window visualization, multiple rounded areas of parenchymal lucency, consistent with

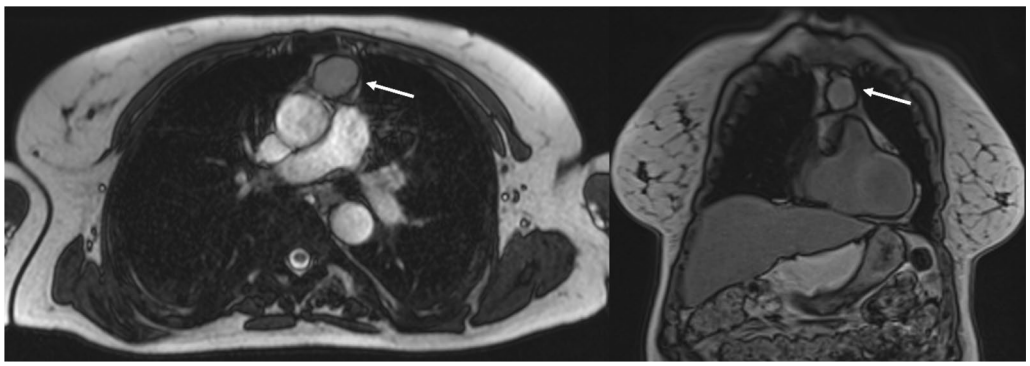

Fig. 1 Axial and coronal magnetic resonance imaging, T2- and T1-weighted images, respectively, demonstrating mediastinal mass in prevascular mediastinal compartment (arrows)

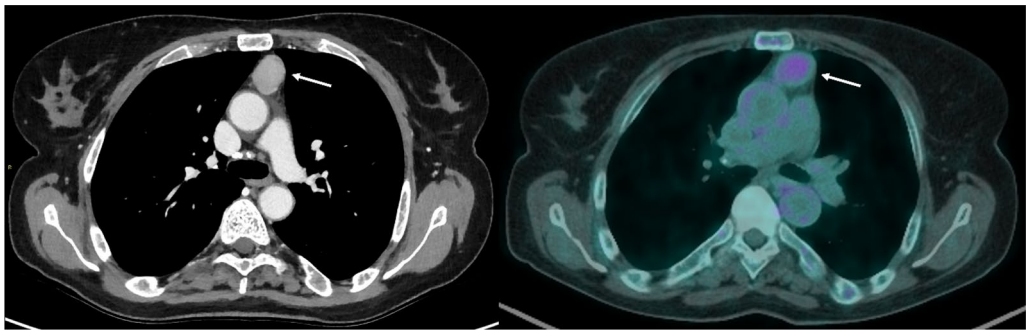

Fig. 2 Chest computed tomography performed after intravenous contrast media administration confirming and more accurately depicting presence of mediastinal mass, which shows mild 18F-deoxyglucose uptake on positron emission tomography-computed tomography imaging (arrows)

thin-walled cysts distributed symmetrically throughout both lungs, with normal intervening parenchyma, were evident (Fig. 3).

No nodules or other interstitial abnormalities were associated with the cysts. No pneumothorax was detected. Coherently with thalassemic bone disease, the ribs appeared widened, and the spine displayed mild platyspondyly. The remaining portion of the chest and visible upper abdomen were unremarkable. The radiological findings were consistent with cystic lung disease, most likely LAM.

The patient was then referred to the pulmonary clinic for further evaluation. She was a never-smoker and did not report any respiratory symptoms. In particular, she denied a history of chronic cough, recurrent respiratory infections, or pneumothorax. No cutaneous lesions, notably facial fibrofolliculomas, were evident. On chest examination, the lung fields were clear. Peripheral capillary oxygen saturation was normal (98%), with a heart rate of 75 beats per minute. Pulmonary function tests revealed a substantial reduction in diffusing capacity of the lungs for carbon monoxide (DL_{CO}; 42% of the predicted value), partly imputable to the condition of anemia, with a carbon monoxide transfer coefficient (KCO) of 73% of the predicted value. After discussion in a multidisciplinary tumor board setting, including a pulmonologist, the patient underwent left thoracoscopic thymectomy and concomitant lingual segment wedge resection. The histopathological report revealed a morphological finding and immunohistochemical pattern referable to type B2 thymoma with focal infiltration of the capsule. Extracapsular extension was not evident. However, the lesion was present at the resection margin (stage IIa according to Masaoka–Koga; stage 1a according to the tumor, node, metastasis [TNM] classification).

Regarding the lung parenchyma, histopathologic analysis described lung parenchyma with cysts of variable size lined by spindle cells in myoid habit with immunohistochemical reactivity for actin, estrogen, progesterone receptors, and HMB45 (focal positivity). Modest chronic

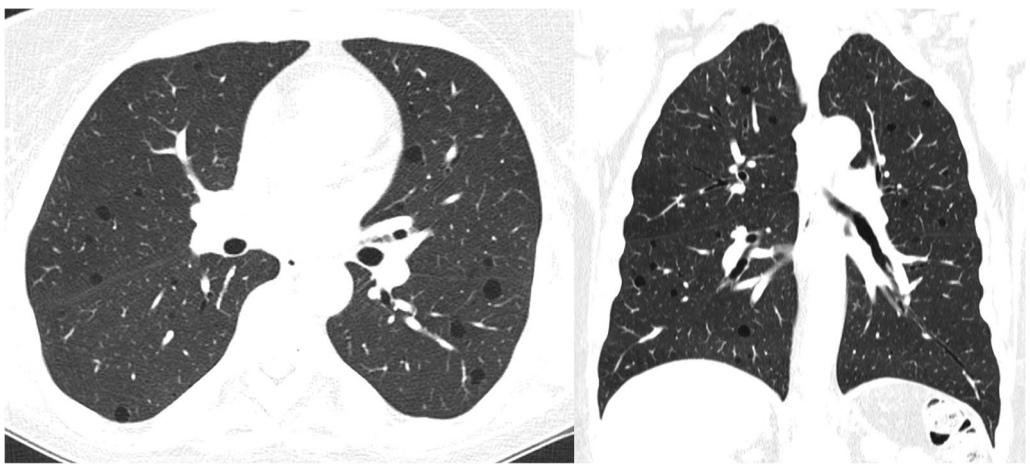

Fig. 3 Chest computed tomography, lung window, displaying multiple lung cysts randomly distributed in both lungs

interstitial inflammation, vascular congestion, and recent blood extravasation were evident. These morphological findings were compatible with pulmonary LAM (Fig. 4).

A final histological diagnosis of thymoma and pulmonary LAM was made. For the neoplastic condition, the patient was a candidate for adjuvant radiation therapy due to the microscopically incomplete resection (R1) [6]. For LAM with concomitant β-thalassemia, treatment with sirolimus was recommended.

Discussion and conclusion

We report the unusual association of thymoma and LAM, both incidentally discovered, in a patient with β-thalassemia major.

Speculatively, patients with thalassemia could indeed be at an increased risk of developing cancer due to various risk factors, in comparison with the general population. These encompass immunologic aberrations and oxidative damage induced by iron overload, immunomodulation resulting from transfusions, viral infections, utilization of hydroxyurea, and stimulation of bone marrow due to chronic anemia [2].

Recent literature supports a well-established correlation between thalassemia and hepatocellular carcinoma [2]. However, the increase in the incidence of other cancers over time and the finding that they have become the second most common cause of death in recent years reflect, at least in part, the observation in the general population of a correlation between age and increasing neoplastic risk.

The case we described is the first in the literature to report the association of a thymoma with β -thalassemia. The available data regarding the descriptive epidemiology of thymoma are limited and yield few clues to the etiology of this malignancy. Indeed, thymic epithelial tumors represent a group of uncommon neoplasms of unknown origin with an estimated incidence of 0.13 to 0.32/100,000, accounting for approximately 0.2–1.5% of all cancers [6, 7]. There is no evidence in the literature supporting a distinct genetic mutation driving the development of thymomas, nor are there definite environmental or occupational exposures associated with an increased risk of these neoplasms [7]. However, due to the complex function of the thymus in the immune system, there have been reports exploring potential connections with various blood diseases, immunosuppression, and infections [6, 7]. Thymomas exhibit a diverse range of clinical manifestations. In one-third of cases, they occur in conjunction with an autoimmune condition, mainly myasthenia gravis, which is more common in type AB, B1, and B2 thymomas and is almost always associated with anti-acetylcholine receptor antibodies. In another one-third of cases, they manifest with local symptoms such as neck mass, chest pain, and superior vena cava syndrome. Lastly, they may be incidentally discovered on chest imaging in an asymptomatic subject as a mediastinal mass [6, 8]. While facing an unexpected anterior mediastinal mass, a presumptive diagnosis is facilitated by clinical judgment derived from a comprehensive history and physical examination, with particular attention to neurological aspects, laboratory tests, and radiological characteristics. The differential diagnosis of anterior mediastinal masses is wide, encompassing tumoral and non-tumoral conditions. Lymphoma may be considered in cases of rapid onset of B-signs and coexistent lymphadenopathies, which were not evident on MRI, despite the incomplete examination with an acquisition protocol optimized for iron quantification, neither on subsequent CT study.

Among the non-neoplastic conditions, in this peculiar clinical context, one should consider the hypothesis of extramedullary hematopoiesis. The most common

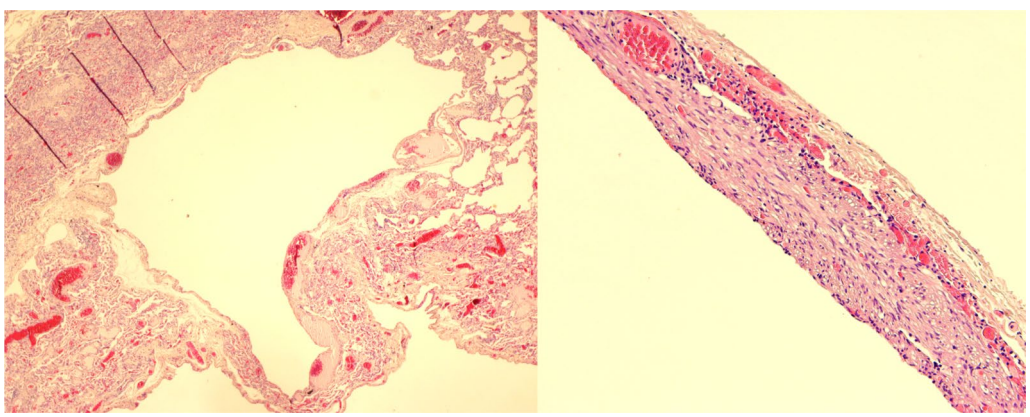

Fig. 4 Histopathology lung specimen, stained with hematoxylin and eosin, showing a parenchymal cyst at low power magnification. In B, the cystic wall expanded by oval to spindle, myoid lymphangioleiomyomatosis cells at 10× magnification

thoracic manifestation of extramedullary hematopoiesis is paraspinal masses, which are typically discovered incidentally, particularly in subjects with thalassemia [9]. The location of the finding in this case makes this diagnosis unlikely.

PET-CT may be used to narrow the differential diagnosis by distinguishing between lymphomas and thymomas, with the first generally showing higher maximum standardized uptake values (SUVmax) [10].

Further, LAM is a rare, slowly progressive, female-predominant, systemic disease characterized by pulmonary cysts, abdominal tumors, and chylous effusions due to the infiltration of neoplastic LAM cells [11].

The incidental finding of multiple lung cysts, consistent with diffuse cystic lung disease, poses the need for an accurate differential diagnosis based on imaging. Diseases or conditions presenting with lung cysts occupy a broad spectrum. The radiologic features of lung cysts, such as their size, wall thickness, number, location, and distribution, along with the accompanying radiologic findings, are the most valuable diagnostic clues for identifying various cystic lung conditions [12, 13]. Lung cysts in LAM are typically round or ovoid in shape, thin-walled, multiple, and diffusely distributed throughout the lungs. The lung parenchyma between cysts is normal, as in this case. However, patients with LAM usually have nonspecific symptoms, including slowly progressive dyspnea, chest pain, cough, wheezing, and recurrent pneumothorax, which were absent in this patient.

It is known that LAM has been included in the family of "perivascular epithelioid cell tumors" (PEComas), a heterogeneous group of mesenchymal tumors composed histologically of perivascular epithelioid cells in which myogenic and melanocytic markers typically coexist [14]. It can be considered a low-grade pulmonary neoplasm that is caused by constitutive activation of the mechanistic target of rapamycin (mTOR) pathway driven by mutations in tuberous sclerosis complex (TSC) genes [15]. LAM can develop in patients with known TSC (TSC-LAM) or sporadically in patients without the inheritable condition (sporadic LAM).

Further confirmatory tests are advisable for patients who have cystic changes on chest CT that are characteristic of LAM but have no additional confirmatory features (that is, presence of tuberous sclerosis complex, angiomyolipomas, chylous effusions, lymphangioleiomyomas, or elevated serum vascular endothelial growth factor-D (VEGF-D) greater than or equal to 800 pg/ml). In our facility, serum VEGF-D concentration test is currently not available. Nevertheless, it is worth noting that the patient exhibited chest CT imaging that was indicative of LAM (more than ten lesions); histological diagnosis was required in the absence of additional clinical manifestations. A further diagnostic approach may consider a transbronchial lung biopsy before a surgical lung biopsy [16]. Given the potential resectability of the mediastinal mass, a surgical lung biopsy may be deemed a valuable option in this case. Confirmation of the diagnosis of LAM was important, as the cystic progression of this disease is known in the literature and could pose a challenge in a patient also having thalassemia.

Symptomatic LAM almost exclusively occurs in women in the fourth to fifth decade of life, usually manifesting with progressive dyspnea or recurrent spontaneous pneumothorax. Given the multisystem nature and relative rarity of LAM, it can be challenging to establish a diagnosis and formulate appropriate management strategies [17]. The American Thoracic Society/Japanese Respiratory Society (ATS/JRS) clinical practical guidelines [18], in cases in which chest CT shows cystic abnormalities indicative of LAM but with no other confirmatory clinical or extrapulmonary radiologic features, suggest performing VEGF-D testing to establish the diagnosis of LAM before proceeding to more invasive investigations. In the case we presented, we decided to perform a surgical lung biopsy directly at the same time as the thymectomy. Indeed, although the accuracy of the diagnosis of LAM based on chest high-resolution CT is deemed high among experts, basing the diagnosis on imaging alone is generally not considered advisable, particularly in the case of a lack of suggestive clinical features, including TSC, renal angiomyolipoma, cystic lymphangioleiomyoma, or chylous effusions in the chest and/or abdomen [18].

Regarding LAM treatment, it was first shown in a pilot study, the Cincinnati Angiomyolipoma Sirolimus Trial (CAST) [19], that sirolimus (which blocks the constitutive activation of rapamycin mTOR) could reduce angiomyolipoma volume and increase functional parameters in patients with LAM. The efficacy of sirolimus in the functional stabilization of FEV1 over 12 months of treatment was also demonstrated [20]. Discontinuation of therapy caused a rapid decline in lung function, similar to that in the placebo group, suggesting the need for continued treatment. The ATS/JRS guidelines recommend sirolimus treatment for patients with impaired lung function, defined as FEV1 less than 70% predicted or patients with progressively declining lung function [18]. Because sirolimus increases fetal hemoglobin levels, it has been recognized as an orphan drug for thalassemia. Two randomized controlled trials [21, 22] showed that everolimus, a second-generation mTOR1 inhibitor, was effective in reducing the size of giant cell astrocytomas in patients with TSC and the size of renal angiomyolipomas in patients with TSC or LAM. The safety profile of everolimus was similar to that of sirolimus in the MILES study.

Serum VEGF-D levels decreased throughout the duration of treatment. Treatment with everolimus resulted in stabilization of FVC and improvement in FEV1, compared with baseline [23]. Patients, however, may be unresponsive or intolerant to mTOR inhibitor treatment or even recur after discontinuation of therapy: these results suggest that mTOR inhibitors are not curative for LAM. Therefore, formulating a correct diagnosis for our patient implied a possible therapeutic opportunity on two fronts.

Several reports exist regarding the association of thymic neoplasms with a variety of conditions classified under "parathymic syndromes," which are acknowledged to have a paraneoplastic/autoimmune etiology [24]. Paraneoplastic syndromes can precede the diagnosis of the thymic tumor and may improve with treatment of the tumor itself. Although myasthenia gravis is the most common among these syndromes, there are others related to hematopoietic cells, including pure red cell aplasia and hypogammaglobulinemia, or to the lung [25]. However, this is the first report describing the association of a thymoma with pulmonary LAM and thalassemia major. Although we cannot ascertain a definitive pathophysiological connection between these conditions from the data at hand, it is intriguing to speculate on a possible common substrate underlying these pathologies in the patient presented in our case study.

In conclusion, survival rates for patients with thalassemia have increased dramatically over the past few decades due to safer transfusion regimens and more effective iron chelation therapy. Because of the increased lifespan, we could expect an increase in the observation of neoplastic conditions due to several predisposing factors. For the first time in the literature, we described the association between thymoma and pulmonary LAM in a relatively young patient with β-thalassemia. This case underlines the importance of sensitizing radiologists to thoroughly review periodic MRIs performed on patients with thalassemia for the purpose of monitoring martial deposits, as such investigations may serendipitously reveal additional pathological conditions.

Abbreviations

^{18}FDG	^{18}F-deoxyglucose
CT	Computed tomography
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
LAM	Lymphangioleiomyomatosis
MRI	Magnetic resonance imaging
PET	Positron emission tomography
TSC	Tuberous sclerosis complex
T1-wi	T1-weighted images
T2-wi	T2-weighted images
VEGF-D	Vascular endothelial growth factor-D

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Author contributions
All authors contributed to the study conception and design. Material preparation and analysis were performed by ACo, LV, FQ, DG, and FL. Data collection was carried out by MC. The first draft of the manuscript was written by ACa and LV, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Ethics approval was waived. Written consent was obtained by the patient.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests related to this work.

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