REVIEW

Thymolipoma – the frontier between hamartoma and neoplasia?

CORNELIA AMĂLINEI[1,2], ADRIANA GRIGORAŞ[1,2], RALUCA ANCA BALAN[1], LAURA ADRIANA RÎŞCANU[1,2], SIMONA ELIZA GIUŞCĂ[1], IRINA-DRAGA CĂRUNTU[1]

[1)]*Department of Morphofunctional Sciences I, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*
[2)]*Department of Histopathology, Institute of Legal Medicine, Iaşi, Romania*

Abstract

Thymolipoma is an uncommon benign thymus lesion, with a partially deciphered etiopathogeny, being most frequently diagnosed in young patients, regardless of gender. Incidentally diagnosed in asymptomatic patients, larger thymolipomas lead to symptoms related to neighboring mediastinal structures compression, with an intensity which is correlated with the mass size. Our review presents the main epidemiological, pathogenic, clinicopathological and morphological characteristics of this rare pathology. Sometimes, thymolipomas may be associated with paraneoplastic syndromes, which are alleviated by the mass complete surgical resection. Imagistics may orientate the diagnosis, which is certified by the microscopic examination of the resection specimens. Extensive thymectomy remains the current therapeutic option and new tools have been developed to increase the accuracy of the surgical procedure to avoid incidental lesions of the important elements of the anterior mediastinum. Although rare, thymolipomas should be considered in the differential diagnosis of mediastinal masses and of paraneoplastic syndromes.

Keywords: thymolipoma, mediastinal tumor, immunohistochemistry.

Introduction

Thymolipomas are relatively rare tumors, representing about 2–9% of thymic neoplasms [1–4] and show a slow development. They have been firstly described in literature by Lange, in 1916, and named "lipoma of the thymus" [5]. The term "thymolipoma" was proposed in 1949, by Hall, who suggested that this lesion is a true mixed tumor of fat and thymic tissue [6]. Thymolipoma is also known as benign thymoma, lipoma of the thymus, thymolipomatous hamartoma, mediastinal lipoma, or lipothymoma [7]. Most frequently located in anterior mediastinum, thymolipoma is diagnosed in patients with ages ranging from two to 67 years, without gender predilection [8, 9]. Microscopy shows a tumor mass composed by mature adipose tissue, without atypia, associated with foci of benign thymic tissue, mainly composed of epithelial cells [4, 10–13].

The symptomatology, acknowledged in approximatively 50% of patients, is closely related to location and the size of the tumor area [14, 15]. These lesions are incidental in asymptomatic patients, being detected in routine chest radiographs [16, 17]. The elective therapy is its surgical resection [9, 15, 18]. A series of theories have been launched during the last century, since its discovery, as attempts to explain their etiopathogeny.

Aim

In this context, our article is reviewing the most recent data regarding thymolipoma's pathogeny and diagnosis.

Thymolipoma incidence and pathogeny

Thymolipoma has an incidence of approximately 0.12 cases per 100 000 inhabitants per year [9, 19, 20].

This lesion occurs more frequently in children and younger adults, being almost equally distributed among genders [15, 21]. Since its first description, in 1916, 122 cases had been reported, 67 of them in males and 55 in females, up to 1993, in patients with ages ranging between three to 76 years (mean 31.1 years), 25 cases being diagnosed in children less than 15 years old [22]. Overall, up to 2011, 200 cases of thymolipoma have been described in literature [23].

Its limited incidence in current practice is supported by the analysis of the publications reporting thymolipomas. Accordingly, 32 new cases of thymolipomas have been identified in articles published *in extenso*, in English language, which provided sufficient descriptive data, in *PubMed*, *Scopus*, and *Web of Science* databases, during 2011–2021 period of time. The gender distribution has been equal (16 males and 16 females), nine cases being children with ages less than 15 years. The patients' age ranged between 6-month-old [18] and 82 years [12], as the extreme ages of patients diagnosed with thymolipoma in the mainstream publications, according to our knowledge (Figure 1).

The rare occurrence of these lesions is also supported by our experience, with a single incidental case in a male of 54 years, necroptically diagnosed [24].

To decipher the origin of this tumor, several theories have been proposed to explain their development. According to the neoplastic theory, thymolipomas are considered mesenchymal tumors (related to the adipocytic component) or a combined neoplasm of neoplastic thymic epithelial and fat components [8, 20]. This theory is based by the identification of enhanced carbohydrate antigen (CA) 19-9

serum levels in some cases of thymolipoma [25, 26]. CA 19-9, normally produced in small quantities by thymus, shows an increased serum level due to the development of the neoplastic thymic component of the thymolipoma [17, 26].
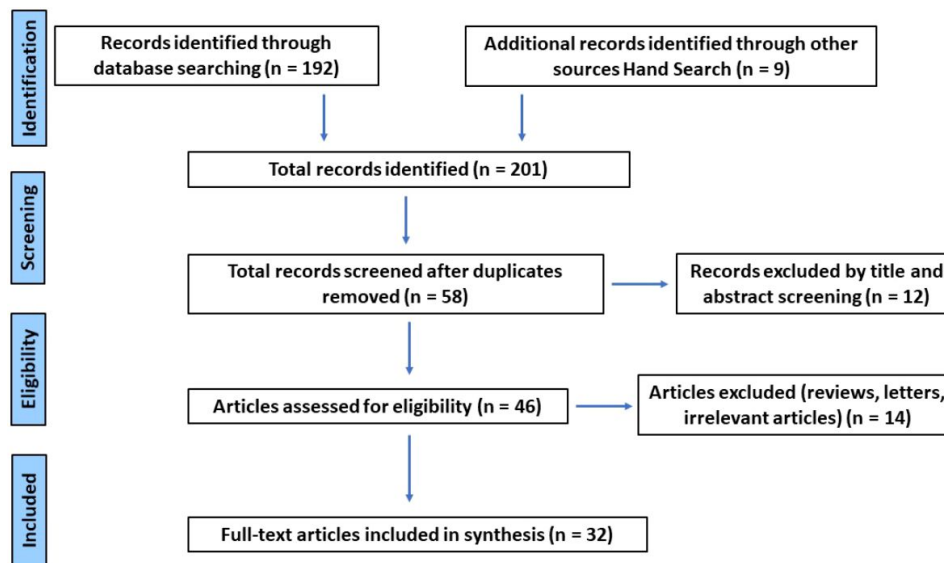

Figure 1 – *Literature search flow diagram; the main reasons for exclusion were the following: non-English language, review-type articles, and irrelevant articles.*

The second theory is suggesting that thymolipomas are thymic hamartomas, formed by an admixture of white adipose tissue (30% to 80%) associated with thymus epithelium [20, 27]. Hamartomas have a slow growth, being able to develop anywhere in the body, but are usually found in the lung, breast, colon, hypothalamus or liver (von Meyenburg complex) [28, 29].

The incidence of most hamartomas is still unknown, except pulmonary hamartoma, which has an incidence of 0.25% [30]. Lung hamartomas are most often incidentally diagnosed after 40 years old, comprising 8% of all lung tumors, sometimes representing necroptical findings [30, 31]. Morphologically, hamartomas have similar features to benign tumors, being characterized by the disorganized growth of the local normal tissues, usually without signs of metastasis or local invasion, such aspects being also observed in thymolipomas. Common histological components of both lung hamartomas and thymolipomas are adipose tissue and epithelium, while the other elements are different.

Sometimes, hamartomas development is associated with phosphatase and tensin homolog (*PTEN*) gene mutation, a gene located on chromosome 10q23, involved in angiogenesis and cell proliferation control *via* downregulation of phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway [32]. Most commonly recognized *PTEN* hamartoma tumor disorders include Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, *PTEN*-related *Proteus* syndrome, and *PTEN*-related *Proteus*-like syndrome, all with a prevalence of 1/200 000 in the general population [32, 33].

Another theory is proposing that thymolipomas are the result of involution of thymic hyperplasia or of a regressed thymoma [8, 17]. In thymic hyperplasia involution, an increased thymic volume beyond the normal level for the patient's age is noticed, because of an expansion of white adipose tissue, which progressively replaces thymus parenchyma [8, 20, 34]. The remnant thymic parenchyma is composed by epithelial cells and thymocytes (immature lymphocytes), sometimes with associated Hassall's corpuscles [20]. Although it is difficult to measure if the thymic volume is larger than normal for the patients' age in medical practice, a normal rim of thymic component at the periphery of the lesion is usually absent in hyperplasia [8, 34].

It should not be overlooked that the thymus has a physiological involution with aging. Its development starts during the sixth week of gestation from the third and fourth pharyngeal pouches, common with that of the inferior parathyroid gland [35]. Its embryologic development in close relation to that of parathyroid is observed in DiGeorge syndrome, which is characterized by complete or partial absence of the third and fourth pharyngeal pouches and their derivatives – the parathyroid glands, thymus, and C-cells [36, 37]. Along with DiGeorge syndrome, thymic cyst, ectopic cervical thymus, hypopharyngeal duct cyst, and the undescended thymus are the most important thymic congenital anomalies with an unknown incidence, considering that these lesions are often asymptomatic [36, 37].

Exceptionally, a thymoma may suffer regression, as it has been mostly observed in thymolipomas associated with *myasthenia gravis* [8, 38].

Cytogenetics data of thymolipomas are limited, with a translocation between chromosomes 12 and 14 in a patient of 27 years, with a 46,XX karyotype, *t*(12;14)(q15q32) [8]. Another mention regarding aberrations/translocation of high mobility group AT-hook 2 (*HMGA2*) gene on chromosome 12q15, which occur in approximately two thirds of lipomas with abnormal karyotypes [15, 39], would suggest the idea that thymolipomas may represent a neoplasm of thymic adipose tissue, associated with areas of thymus parenchyma showing a normal or a regressed appearance [8, 15, 40].

⊡ Thymolipoma symptoms and diagnosis

Most patients diagnosed with thymolipoma are asymptomatic, being incidentally diagnosed during a

routine thoracic X-ray [27, 41, 42] or even during autopsy [24].

When symptomatic, thymolipomas are manifested by signs of local compression by the tumor-like mass. Patients may accuse dyspnea, chest pain, weight loss, upper respiratory infections, chronic cough, or nausea and vomiting due to esophageal compression [8, 19, 43–46]. Thymolipomas may also lead to heart compression, followed by chronic heart failure [47].

Additionally, some patients with thymolipoma may have symptoms associated to paraneoplastic syndromes, such as *myasthenia gravis*, Graves' disease, hypogamma-globulinemia, aplastic anemia, and lichen planus [15].

Thymolipoma–*myasthenia gravis* association is registered in approximately 2.8% to 50% of patients [15, 48], being mainly observed in older people [46, 48], which have autoantibodies against post-synaptic acetylcholine receptor (AChR Abs) [49]. However, according to data published by Poursadeghfard *et al.*, in a 24-year-old patient diagnosed with thymolipoma-associated *myasthenia gravis*, AChR Abs have been absent but a high serum level of muscle-specific kinase (MuSK) has been detected [50]. While MuSK involvement in postsynaptic membrane support, with AChR clustering in the neuromuscular junction is known, the mechanism of thymus tissue initiation of MuSK serum increase is not completely deciphered [50].

It has been also noticed that some patients may develop a progressive anemia [46], probably induced by an auto-immune erythroid precursor destruction, according to Ferreira *et al.*, who noticed a total anemia remission after thymolipoma surgical excision, in a 73-year-old patient [16]. The correlation between thymolipoma and blood cells count is also supported by another recent report, with normalization of lymphocytes count after surgical resection, in an 8-year-old female patient showing lympho-cytosis, with normal lymphocyte morphology, 80% of them belonging to T-lymphocytes type [21].

Exceptional cases have been reported in literature, such as a thymoma development within a thymolipoma [51, 52] and an association between thymolipoma and thyrolipoma (adenolipoma of thyroid), with or without pharyngeal lipoma [53–55]. Although they are distinctive lesions, thymolipoma and thyrolipoma exhibit histopatho-logical similitudes, suggesting a common etiology. According to Trites's hypothesis, in these cases, a disturbance in the primitive foregut early development takes place, considering the common origin of both thymus and thyroid [54].

Thymolipomas diagnosis certification is based on microscopy, performed in most cases after the surgical excision of the mediastinal tumor mass. However, pre-operative imagistic, such as chest radiography (X-ray), thoracic computed tomography (CT) or magnetic resonance imaging (MRI) may orientate the diagnosis [56–58]. Thus, thymolipomas show typical well-delimitated, bulky, pendulous, teardrop-shaped, radiolucent mass, in anterior mediastinum on chest X-rays [15, 59], with a changing shape when patient's position is modified [59]. Routine chest X-ray allows the identification of small size thymo-lipomas, in asymptomatic patients, while large thymolipomas may show a radiographic image resembling that of cardio-megaly, lipoma, pulmonary sequestration, or pericardial effusion [15, 59].

Thoracic CT provides valuable information regarding the location and structure of these tumor masses, such as their connection to the thymus anatomic region and its fat density, associated with strands of soft tissue [15, 51]. These features are supplemented by MRI data, characterized by tumor masses of high signal intensity equal to fat on T1-weighted images and T2-weighted images, with areas of intermediate signal intensity corresponding to thymic tissue or fibrous areas [18, 59].

Aside controversies, preoperative microscopic exam may be performed using fine-needle biopsy aspirate (FNAB), although not recommended in all patients' protocol. This examination limits are highlighted by false positive results for malignancy, as in a 24-year-old patient who has been initially diagnosed by FNAB with well-differentiated liposarcoma instead of thymolipoma [60].

⚑ Thymolipoma morphology

Thymus is an encapsulated, bilobed organ, located in the anterior mediastinum, with 10–15 g weight at birth [61]. Physiologically, it is developing until puberty, when it reaches a weight of 34±10 g [61]. Following this age, a slow replacement of the thymic parenchyma with adipose tissue is preventing its microscopical recognition [61].

Thymolipomas occur most frequently in the cardio-phrenic angle [62], often as large tumor masses, with an average up to 20 cm in diameter [63] and a weight over 500 g (70% of cases), at diagnosis [59]. The maximum weight of thymolipomas can be up to 16 kg, while a normal thymus of a 30-year-old patient weighs only about 25 g [27, 48].

According to Kitano *et al.*, the weight of thymolipomas diagnosed in 122 patients included in an investigated group had a variable value, between 154 to 2235 g (mean, 709 g) [22]. According to our data regarding the thymolipomas weight measured in the 32 patients included in our group of study, it ranged between 40 g and 6000 g (mean about 2285 g).

Small size lesions maintain their location in the anterior mediastinum, while larger thymolipomas grow downward in a pedunculated fashion toward the diaphragm, sometimes covering the heart or insinuating itself between the heart, lungs, and diaphragm [59]. They may also adhere to pericardium or pleura [59]. Exceptionally rare, they may be located in the anterosuperior mediastinum or in the posterior mediastinum [59].

Macroscopically, thymolipomas are yellow masses with well-defined borders, a capsule, and lobulated contours [5, 43]. They exhibit a yellow, soft, homogeneous consistency on the section surface and generally do not show areas of necrosis or hemorrhage [5].

Microscopically, they are comprised of mature white adipose tissue, without cytological atypia or mitotic activity, associated with remnants of thymic tissue [4, 15]. The adipose tissue content of thymolipomas usually represents 50–85% of the lesion, but it has been reported to account for as much as 95% of the lesion [62]. The thymic tissue component may be variable, from strands of atrophic thymus epithelium to large areas containing inconspicuous normal thymic parenchyma, with Hassall's corpuscles [15, 64] (Figures 2 and 3). Few myoid cells may by rarely identified

and malignant transformation or invasion has not been reported until now [8]. The origin of thymic myoid cells may be represented by the metaplastic change of reticulo-epithelial thymic cells, or from perithymic mesenchymal cells incorporated into the thymus, or from cells of the neural crest [65].

Added to the classical type of thymolipoma, other variants are described, such as thymofibrolipoma [66, 67]
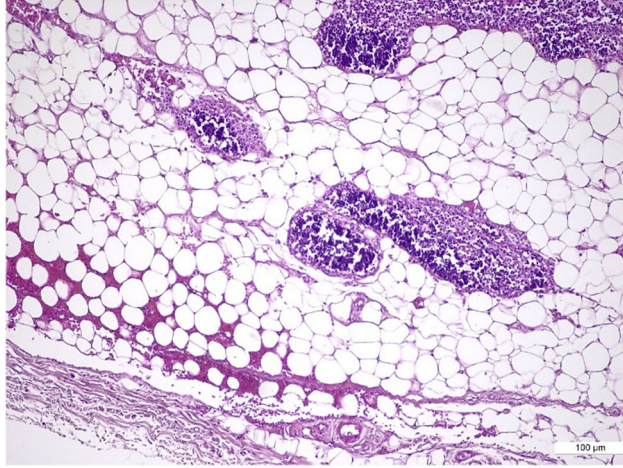
and thymoangiolipoma [15, 68]. Extensive areas of thick collagen fibers associated with islands of mature white adipose tissue are detected in thymofibrolipomas [67], while a variable proportion of mature fat tissue, thymic component, and blood vessels are observed in thymo-angiolipomas [15]. In some cases, as in normal thymus, striated skeletal muscle or "myoid" cells may be detected in thymolipomas [20] (Figure 4).

Figure 2 – *General view of thymolipoma, exhibiting thymic areas within adipose tissue mass, lined by a capsule. Hematoxylin–Eosin (HE) staining, ×40.*
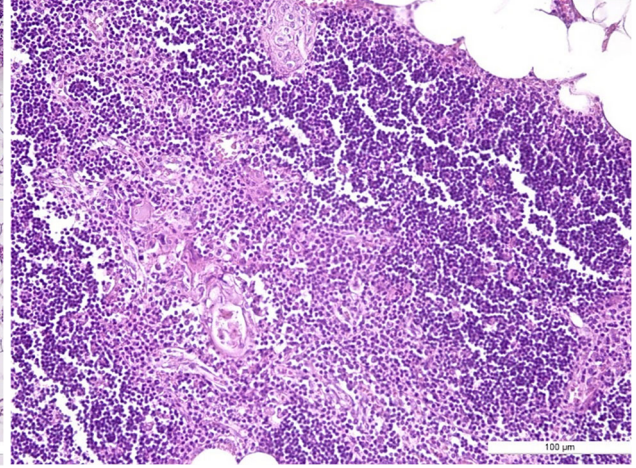

Figure 3 – *Thymic component of thymolipoma, showing cortex and medulla containing Hassall's bodies. HE staining, ×200.*
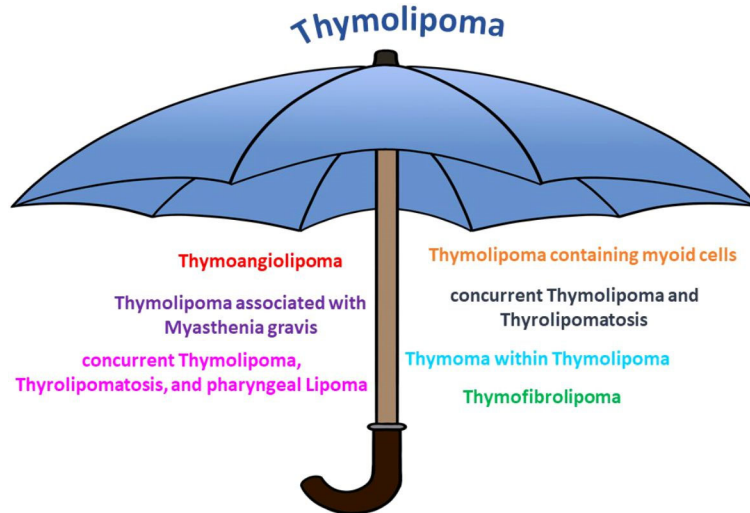

Figure 4 – *Thymolipoma spectrum; added to common type of thymolipoma, thymofibrolipoma, and thymoangiolipoma represent rare lesions; occasionally, thymoma may develop within a thymolipoma or thymolipoma may be associated to thyrolipoma.*

Immunohistochemical pattern of thymolipoma is characterized by mouse double minute 2 homolog (MDM2) negativity [4]. No cyclin-dependent kinase (CDK) 4 expression is evident in adipocytes, while cluster of differentiation (CD)1a, CD99, and terminal deoxynucleotid transferase (TdT) are highlighting the thymic lymphoid (immature) cells (Figures 5 and 6). Additionally, immuno-staining for pan-cytokeratin (CK) AE1/AE3 and p63 or CK5/6, as immunomarkers of squamous differentiation, are positive in the normal thymic epithelium (Figures 7–10) [3]. If striated myoid cells are added in the cellular population of thymolipomas, they show myoglobin and desmin positivity, although they are negative for alpha-smooth muscle actin (*α*-SMA) [65].

⯐ Thymolipoma differential diagnosis

Thymolipomas differential diagnosis includes other mediastinal tumor and tumor-like masses, such as lipoma, lipomatosis of mediastinum, thymic hyperplasia, Morgagni hernia, thymoma, mature teratoma, including malignant neoplasms, such as liposarcoma, lymphoma, and thymic carcinoma [4, 8, 22, 69, 70].

The differential diagnosis between thymolipoma and lipoma is sometimes difficult. Generally, lipomas are large-size masses, located just above the diaphragm. In these instances, the identification of areas of thymic epithelial cells, which are absent in lipoma, added to immunohisto-chemistry, using markers such as CK and p63, is facilitating the thymolipoma diagnosis [15, 71–74].
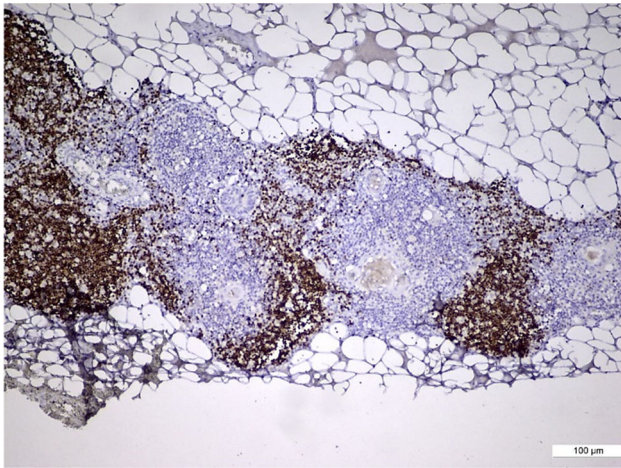
Figure 5 – *Focal TdT positivity in thymic component. Anti-TdT antibody immunostaining, ×40. TdT: Terminal deoxynucleotidyl transferase.*

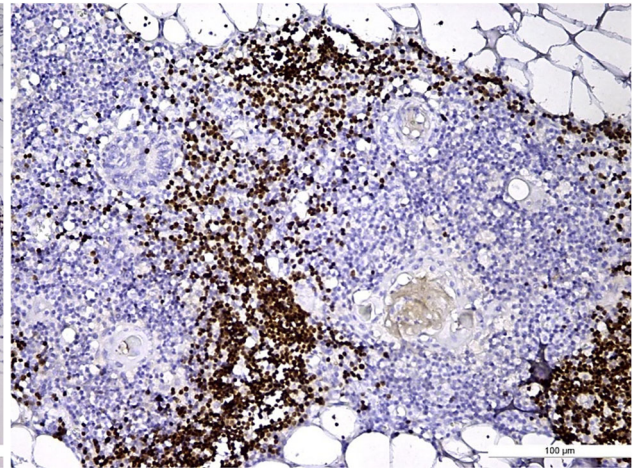

Figure 6 – *Hassall's corpuscles surrounded by areas exhibiting focal TdT positivity (detail). Anti-TdT antibody immunostaining, ×200.*
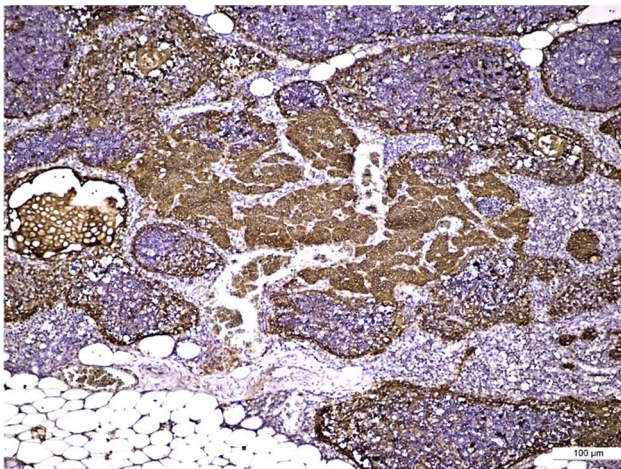

Figure 7 – *Positivity of pan-CK AE1/AE3 in thymic components. Anti-pan CK AE1/AE3 antibody immuno-staining, ×40. CK: Cytokeratin.*
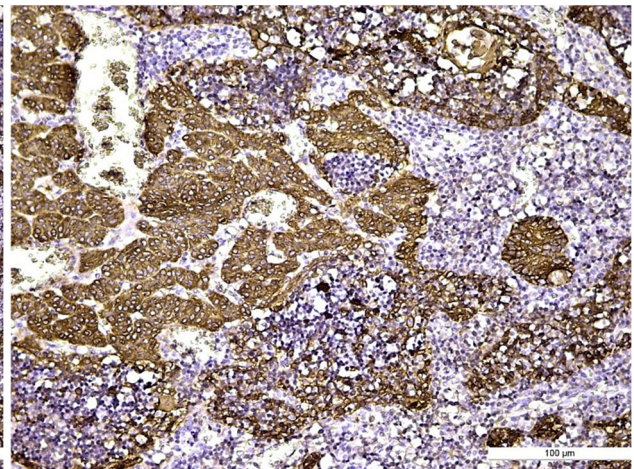

Figure 8 – *Strong positivity of pan-CK AE1/AE3 in the epithelial thymic component (detail). Anti-pan-CK AE1/AE3 antibody immunostaining, ×200.*
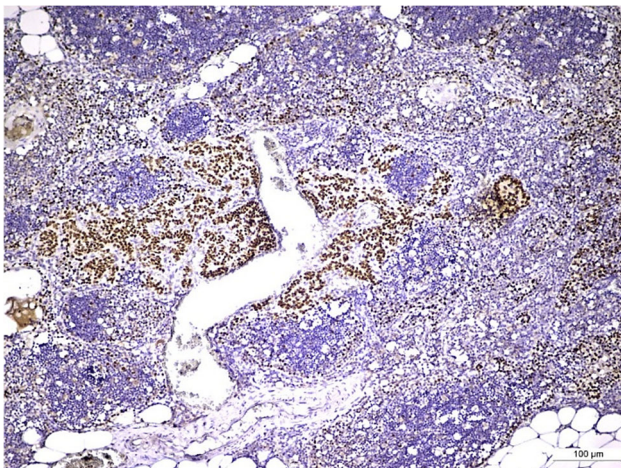

Figure 9 – *Variable positivity for p63 in thymic component. Anti-p63 antibody immunostaining, ×40.*
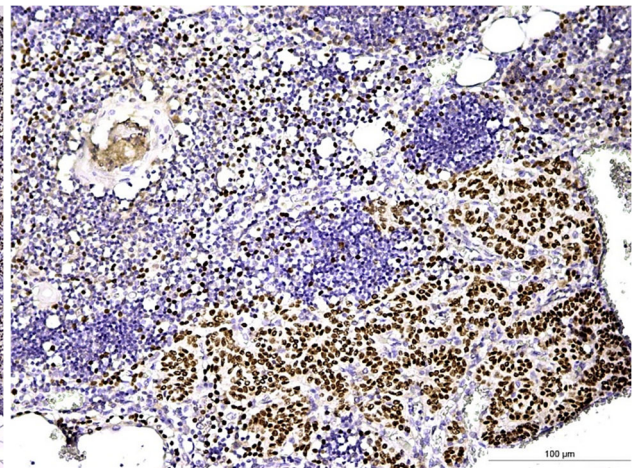
Figure 10 – *Hassall's corpuscle surrounded by cells exhibiting variable positivity for p63. Anti-p63 antibody immunostaining, ×200.*

Furthermore, in practice the differentiation between thymolipoma and mediastinal lipomatosis, a benign condition characterized by mediastinal accumulation of a large amount of mature fat tissues that may infiltrate skeletal muscle, without thymic parenchyma is a clue of diagnosis [75, 76].

Thymic hyperplasia represents thymic enlargement above normal limits for the corresponding age. Criteria such as capsule, dominant proportion of adipose tissue and of a peripheral rimming of normal thymus, are elements which support the diagnosis of thymolipoma against that of thymic hyperplasia [15, 77].

The differential between thymoma and thymolipoma is sometimes difficult. In these situations, the epithelial component is identified by characteristic immunomarkers, such as pan-CK AE1/AE3 and CK7 positivity, added to variable B-cell lymphoma 2 (Bcl-2) positivity, while CK20 and paired box 8 (PAX8) are negative [65, 78, 79]. Extremely rare, unusual associations have been reported in literature, such as thymolipoma and thymoma [50, 80, 81], thymoma and thymic carcinoma arising in a thymolipoma [82], instances that result in a high degree of differential diagnosis difficulty.

Mature teratoma is a mediastinal germ cell tumor, which may develop in anterior mediastinum. This may exhibit areas of white adipose tissue often associated with residual thymic tissue, and thus must be differentiated from thymolipoma. In this direction, the identification of sebaceous glands, cartilage, with or without gastrointestinal and respiratory epithelium may orientate the diagnosis towards a teratoma [15, 65, 71].

The differential diagnosis between thymolipoma and anterior mediastinum liposarcoma is facilitated by criteria that support the diagnosis of sarcomatous malignancy, such as size, myxoid degeneration, lipoblasts, and atypical spindle cells identification [15, 20, 73, 83].

Lymphomas of the mediastinum can originate either from the lymph nodes or the thymus. These display similar morphological and molecular features to their counterparts with other locations [84, 85].

Moreover, the differentiation between thymolipoma and a thymic carcinoma should be performed. Features, such as a non-encapsulated, firm mass, with gray-white cut surface, comprised of malignant cell exhibiting vesicular or hyperchromatic nuclei, with prominent nucleoli are orientating the diagnosis towards a thymic carcinoma. Immunohistochemically, the carcinoma cells are positive for pan-CK AE1/AE3, CD5, CK19 or CD70, but are negative for vimentin, CD99, and CD30 [79, 82, 86, 87] (Table 1).

⌗ Thymolipoma treatment

The curative treatment of thymolipomas consists of complete resection of the tumoral mass by thoracotomy, sternotomy or video-assisted thoracoscopy, according to its location and size [21, 88] (Table 2).

Table 1 – *Differential diagnosis in thymolipomas*

| | Main macroscopic features | Main microscopic characteristics | Gene anomalies | IHC markers | | References |
				Positive	*Negative*	
Lipoma	▪ large size masses ▪ soft, lobular ▪ whitish/yellowish in color	▪ WAs and thin fibrous septa	▪ *HMGA2* ▪ *HMGIC*	▪ leptin ▪ spindle cell type (CD34, S100, vimentin)	▪ p16 ▪ MDM2	[72–74]
Lipomatosis of mediastinum	▪ large amount of non-encapsulated mature fat tissues	▪ sheets and lobules of WAs that may infiltrate skeletal muscle	▪ *PTEN*	–		[76]
Thymic hyperplasia	▪ thymus larger than normal limits for age (based on tables)	▪ normal thymic morphology	–	▪ p63	▪ XIAP	[15, 77]
Morgagni hernia	▪ diaphragmatic hernias (anterior lateral and anterior parasternal defects)	–	▪ trisomy 21 (Down syndrome)	–		[69]
Thymoma	▪ lobulated ▪ grey-tan color ▪ often encapsulated ▪ variable cystic changes	▪ lobulated architecture ▪ neoplastic epithelial cells (polygonal or spindled) ▪ variable numbers of lymphocytes (thymocytes) ▪ sometimes cyst(s) or focal cystic changes	▪ *TMB* ▪ *LOH* ▪ *FOXC1* ▪ *GTF2I* ▪ *HRAS* ▪ *NRAS* ▪ *TP53* ▪ *SMARCB1*	▪ keratins (pan-CK AE1/AE3, CAM5.2, CK7) ▪ squamous differentiation (p40, p63, CK5/6) ▪ Bcl-2 variable ▪ TTF1 (rare in type A thymoma) ▪ thymocytes (TdT, CD1a, CD99)	▪ CK20 ▪ PAX8	[65, 78, 79]
Mature teratoma	▪ encapsulated masses ▪ cut surface with cystic spaces with fluid or hair, fat, bone, and cartilage	▪ haphazard admixture of mature tissues derived from 2 or 3 germinal layers	▪ classical or mosaic Klinefelter syndrome (47, XXY)	▪ to describe the nature of immature components		[15, 65, 71]
Liposarcoma (well differentiated or dedifferentiated variant)	▪ large ▪ relatively circumscribed ▪ areas of necrosis and hemorrhage	▪ mature adipocytes, atypical spindle cells and multivacuolated lipoblasts in a myxoid to dense fibrous stroma	▪ *MDM2* ▪ *CDK4* ▪ *HMGA2* ▪ *TSPAN31* ▪ *OS1/9* ▪ *STAT6* ▪ *GLI1* ▪ *CHOP*	▪ MDM2 ▪ CDK4 ▪ S100 ▪ p16	▪ HMB45 ▪ CD34 ▪ keratins ▪ desmin ▪ actin	[20, 73, 83]
Lymphoma	▪ infiltrative mass ▪ fleshy appearance on cut surface ▪ often with necrotic areas ▪ thymic cysts (may be present)	▪ similar to their counterparts presenting in other sites	▪ similar to their counterparts presenting in other sites	▪ similar to their counterparts presenting in other sites		[84, 85]

	Main macroscopic features	Main microscopic characteristics	Gene anomalies	IHC markers		References
				Positive	*Negative*	
Thymic carcinoma	▪ unencapsulated ▪ no internal fibrous septation ▪ necrosis and hemorrhage	▪ variable according to *WHO* classification	▪ *CDKN2A/2B* ▪ *SETD2* ▪ *CYLD* ▪ *TP53* ▪ *ALK* ▪ *FGFR3* ▪ *NRAS* ▪ *HRAS* ▪ *AKT1/2* ▪ *KIT* ▪ *PTEN*	▪ keratins (pan-CK AE1/AE3) ▪ CK18 ▪ CK19 ▪ CD70 ▪ CD5 ▪ GLUT-1 ▪ c-kit ▪ MUC1 ▪ EMA ▪ CEA (variable)	▪ vimentin ▪ CD99 ▪ CD30	[79, 82, 86, 87]

AKT1/2: AKT serine/threonine kinase 1/2; *ALK*: Anaplastic lymphoma kinase; Bcl-2: B-cell lymphoma 2; CD: Cluster of differentiation; CDK4: Cyclin-dependent kinase 4; *CDKN2A/2B*: Cyclin-dependent kinase inhibitor 2A/2B; CEA: Carcinoembryonic antigen; *CHOP*: C/EBP homologous protein; CK: Cytokeratin; c-kit: Tyrosine protein kinase KIT; *CYLD*: CYLD lysine 63 deubiquitinase; EMA: Epithelial membrane antigen; *FGFR3*: Fibroblast growth factor receptor 3; *FOXC1*: Forkhead box C1; *GLI1*: Glioma-associated oncogene homolog 1; GLUT-1: Glucose transporter 1; *GTF2I*: General transcription factor IIi; HMB45: Human melanoma black 45; *HMGA2*: High-mobility group AT-hook 2; *HMGIC*: High-mobility group protein isoform C; *HRAS*: HRas proto-oncogene, guanosine triphosphatase (GTPase); IHC: Immunohistochemistry; *KIT*: KIT proto-oncogene, receptor tyrosine kinase; *LOH*: Loss of heterozygosity; *MDM2*: Mouse double minute 2 homolog; MUC1: Mucin 1, cell surface associated; *NRAS*: Neuroblastoma RAS viral oncogene homolog; *OS1/9*: OS1/9 endoplasmic reticulum-associated lectin; p16: p16 protein; p40: p40 structural glycoprotein; p63: p63 tumor protein; PAX8: Paired box 8; *PTEN*: Phosphatase and tensin homolog; S100: S100 protein; *SETD2*: SET domain containing 2, histone lysine methyltransferase; *SMARCB1*: Switch/sucrose nonfermenting (SWI/SNF)-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1; *STAT6*: Signal transducer and activator of transcription 6; TdT: Terminal deoxynucleotidyl transferase; TMB: Tumor mutational burden; *TP53*: Tumor protein p53; *TSPAN31*: Tetraspanin 31; TTF1: Thyroid transcription factor 1; WAs: White adipocytes; *WHO*: World Health Organization; XIAP: X-linked inhibitor of apoptosis protein.

Table 2 – *Review of thymolipomas reports*

Case No.	Sex	Age [years]	Symptoms and signs	Imaging	Size [cm]	Weight [g]	Associated manifestations	Surgical approach	Reference
1.	M	35	Mild chest discomfort	Rx & CT	N/A	2585	No	Surgical excision	[23]
2.	M	49	Weakness and shortness of breath	Rx & CT	34.3×23.4×14.6	4100	B1, B2, and B3 thymomas	Surgical excision	[51]
3.	M	54	Asymptomatic	Rx & CT	12×10×3.5	N/A	No	Surgical excision	[65]
4.	F	29	Progressive dyspnea	CT	N/A	6000	No	Surgical excision	[5]
5.	M	21	Incidentally detected	Rx & CT	16×10×15	1800	No	Surgical excision	[5]
6.	F	78	Persistent cervical pain and postprandial nausea and vomiting	CT & PET	21×17×5	903	No	Surgical excision	[43]
7.	M	35	Chest pain	Rx & CT	4×6×12	N/A	No	Surgical excision	[10]
8.	M	11	Recurrent chest pain	CT	5.2×4.1×2	N/A	No	Surgical excision	[41]
9.	M	0.5	Rapid breathing for the previous three months	CT	N/A	840	No	Surgical excision	[18]
10.	M	11	Painless progressively growing right cervical mass	Rx & CT	17×9×3	1800	No	Surgical excision	[42]
11.	F	27	Breathlessness on exertion	Rx & CT	40×30×10	4500	No	Surgical excision	[44]
12.	F	2	Mild biphasic stridor	CT	14×10×7	354	No	Surgical excision	[45]
13.	F	30	Shortness of breath	CT	20×17×15 (part 1) and 28×25×17 (part 2)	4150	Gardner's syndrome	Surgical excision	[11]
14.	F	59	Dyspnea	CT	39	2800	B3 thymoma	Surgical excision	[52]
15.	F	82	Mild dyspnea and dysphagia	Rx & CT	7.4×6.6×9.5	N/A	No	No consent for surgery	[12]
16.	F	17	Progressive dyspnea and nonproductive cough	Rx & CT	12×10×8	N/A	No	Surgical excision	[56]
17.	M	40	Progressive dyspnea	Rx & CT	40×33×8	N/A	No	Surgical excision	[57]
18.	M	68	Effort intolerance and fatigue	CT	N/A	N/A	No	Surgical excision	[1]
19.	M	35	Chest pain, cough, dyspnea	Rx & CT	31×21×8	5000	No	Surgical excision	[13]
20.	M	73	Progressive shortness of breath	CT	N/A	N/A	Pure red cell aplasia and Klinefelter syndrome	Surgical excision	[16]
21.	F	4	Intermittent low-grade fever and cough	Rx & CT	10	N/A	No	Surgical excision	[14]
22.	M	3	High fever and productive cough	Rx & CT	8×5×3.5	N/A	No	Surgical excision	[17]
23.	F	24	Ptosis, dysphagia, dyspnea, and generalized weakness	CT	0.7×0.6	N/A	*Myasthenia gravis*	Surgical excision	[50]

Case No.	Sex	Age [years]	Symptoms and signs	Imaging	Size [cm]	Weight [g]	Associated manifestations	Surgical approach	Reference
24.	M	23	Cough and dull ache pain	Rx & CT	26×18×11	6000	No	Surgical excision	[3]
25.	F	6	Dry cough	Rx & CT	13×16×16	N/A	Lymphocytosis (normal lymphocyte morphology)	Surgical excision	[21]
26.	M	61	Right eye ptosis	Rx	8×7×3	150	*Myasthenia gravis*	Surgical excision	[15]
27.	F	60	Dyspnea, chest pain, and nonproductive cough	CT & TE	N/A	N/A	No	No consent for surgery	[58]
28.	F	56	Acute congestive heart failure, atrial fibrillation, and stroke secondary to infected vegetation from the mitral valve	CT	7×3×1.5 (left lobe) and 9×3×1.8 (right lobe)	40	*Myasthenia gravis*	Surgical excision	[46]
29.	M	8	Syncopal episode	Rx & CT	N/A	N/A	No	Surgical excision	[88]
30.	F	66	Progressive shortness of breath, palpitations, unintentional weight loss	Rx & CT	N/A	N/A	No	Surgical excision	[4]
31.	F	64	Dyspnea	CT & PET–CT	N/A	N/A	Thyrolipoma and *myasthenia gravis*	Surgical excision	[55]
32.	F	8	Breathlessness and cough	Rx, CT & MRI	16×11.5×10.5	N/A	No	Surgical excision	[70]
33.	M	56	N/A	N/A	1.9×2×2	N/A	No	Autopsy dissection	[24]

CT: Computed tomography; F: Female; M: Male; MRI: Magnetic resonance imaging; N/A: Not available; PET: Positron emission tomography; Rx: Thoracic radiography; TE: Thoracic echocardiography.

The difficulty of surgical intervention is depending on the tumor size and on the anatomic characteristics of the mediastinum. In this direction, a recent study revealed that the resection of thymic tumors by robotic surgery is safe, in perspective of precise dissection of mediastinum elements, particularly of those situated at the thymus superior poles [9]. Thus, this resection method allows not only the limitation of postsurgical complications, but also the reduction of the hospitalization period [9].

Thymolipomas do not exhibit recurrences after the surgical resection, thus the follow up is not necessary. Moreover, the remission of associated paraneoplastic syndromes, such as *myasthenia gravis*, after thymus resection is also reported [40].

⊡ Conclusions

Thymolipoma is a rare benign lesion among the tumoral pathology of the anterior mediastinum, being composed by an admixture of mature white adipose tissue and thymic tissue. Thymolipoma has a slow growth, leading to the possibility to reach a large size at the moment of diagnosis. Occasionally, they may represent incidental forensic findings due to their asymptomatic development. Usually, thymo-lipoma diagnosis is suspected by CT and MRI imagistic findings, being certified by microscopic examination of the surgical resection specimen. Despite their rarity, thymo-lipomas must be considered in the differential diagnosis of masses of the anterior mediastinum.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Goswami A, Baruah AR. Giant thymolipoma: a rare case presentation. Asian Cardiovasc Thorac Ann, 2017, 25(2): 143–145. https://doi.org/10.1177/0218492315599689 PMID: 26265159

[2] Ruffini E, Filosso PL, Guerrera F, Lausi P, Lyberis P, Oliaro A. Optimal surgical approach to thymic malignancies: new trends challenging old dogmas. Lung Cancer, 2018, 118:161–170. https://doi.org/10.1016/j.lungcan.2018.01.025 PMID: 29571996

[3] Sharma KC, Bhakuni YS, Darlong LM, Pasricha S, Dewan AK, Chand R, Goswami P, Rajappa SK. A giant mediastinal thymolipoma: a rare pathological entity. Indian J Thorac Cardiovasc Surg, 2019, 35(1):115–117. https://doi.org/10.1007/s12055-018-0700-9 PMID: 33060988 PMCID: PMC7525879

[4] Shrivastava T, Ntiamoah P. Rare cause of large anterior mediastinal mass – thymolipoma. Radiol Case Rep, 2020, 15(9):1538–1540. https://doi.org/10.1016/j.radcr.2020.06.044 PMID: 32670456 PMCID: PMC7338678

[5] Reddy RHV, Qureshi NJ. Unusual mediastinal tumour of thymic origin. Indian J Surg Oncol, 2013, 4(3):320–321. https://doi.org/10.1007/s13193-013-0252-9 PMID: 24426748 PMCID: PMC3771060

[6] Hall GFM. A case of thymolipoma with observations on a possible relationship to intrathoracic lipomata. Br J Surg, 1949, 36(143):321–324. https://doi.org/10.1002/bjs.18003614318 PMID: 18113288

[7] Roque C, Rodríguez P, Quintero C, Santana N, Hussein M, Freixinet J. [Giant thymolipoma]. Arch Bronconeumol, 2005, 41(7):402–403. https://doi.org/10.1016/s1579-2129(06)60250-4 PMID: 16029736

[8] Hudacko R, Aviv H, Langenfeld J, Fyfe B. Thymolipoma: clues to pathogenesis revealed by cytogenetics. Ann Diagn Pathol, 2009, 13(3):185–188. https://doi.org/10.1016/j.anndiagpath.2008.02.006 PMID: 19433298

[9] Terra RM, Milanez-de-Campos JR, Haddad R, Trindade JRM, Lauricella LL, Bibas BJ, Pêgo-Fernandes PM. Robotic thoracic surgery for resection of thymoma and tumors of the thymus: technical development and initial experience. J Bras Pneumol, 2019, 46(1):e20180315. https://doi.org/10.1590/1806-3713/e20180315 PMID: 31851218 PMCID: PMC7462674

[10] Döngel I, Imamoğlu H, Şahin AF, Yıldırım S, Bayram M. A rare mediastinal tumor: thymolipoma. Eur J Gen Med, 2014, 11(Suppl 1):21–23. https://doi.org/10.15197/sabad.1.11.23 https://www.ejgm.co.uk/article/a-rare-mediastinal-tumor-thymolipoma-7195

[11] Pei G, Han Y, Zhou S, Liu Z. Giant mediastinal thymolipoma in a patient with Gardner's syndrome. Thorac Cancer, 2015, 6(6):808–811. https://doi.org/10.1111/1759-7714.12231 PMID: 26557924 PMCID: PMC4632938

[12] Kucuk C, Arda K, Ata N, Turkkani MH. Atypical presentation of thymolipoma. Chest Dis Rep, 2016, 4(1):5634. https://doi.org/10.4081/cdr.2016.5634 https://www.pagepressjournals.org/index.php/chest/article/view/5634

[13] Aghajanzadeh M, Asgary MR, Mesbah A, Hemmati H, Delshad MSE, Samidoust P, Hemmati G. Giant thymolipoma of mediastinum and neck – initially misdiagnosed as liposarcoma by core needle biopsy. J Family Med Prim Care, 2018, 7(5): 1079–1082. https://doi.org/10.4103/jfmpc.jfmpc_228_17 PMID: 30598961 PMCID: PMC6259522

[14] Miranda A, Marques J, Ferreira J, Cunha F, Ribeiro M, Ruivo R. Persistent radiologic thoracic hypotransparency: a case report and review of the literature. Arch Pediatr, 2018, 25(8):489–492. https://doi.org/10.1016/j.arcped.2018.09.010 PMID: 30361084

[15] Anbardar MH, Amirmoezi F, Amirian A. Thymoangiolipoma: a rare histologic variant of thymolipoma in a patient with myasthenia gravis. Rare Tumors, 2020, 12:2036361320979215. https://doi.org/10.1177/2036361320979215 PMID: 33489056 PMCID: PMC7768564

[16] Ferreira D, Ponraj R, Yeung A, de Malmanche J. Pure red cell aplasia associated with thymolipoma: complete anaemia resolution following thymectomy. Case Rep Hematol, 2018, 2018:8627145. https://doi.org/10.1155/2018/8627145 PMID: 30402302 PMCID: PMC6198544

[17] Furukawa T, Sakai K, Higashi M, Fumino S, Aoi S, Tajiri T. Thoracoscopic resection for mediastinal thymolipoma in a child. Asian J Endosc Surg, 2019, 12(2):218–221. https://doi.org/10.1111/ases.12627 PMID: 29963757

[18] Parakh A, Singh V, Subramaniam R, Narula MK, Agarwala SK, Shukla S. Giant thymolipoma in an infant. Paediatr Int Child Health, 2014, 34(3):230–232. https://doi.org/10.1179/20469 05513Y.0000000108 PMID: 24621238

[19] Gamondès JP, Balawi A, Greenland T, Adleine P, Mornex JF, Zhang J, Maret G. Seventeen years of surgical treatment of thymoma: factors influencing survival. Eur J Cardiothorac Surg, 1991, 5(3):124–131. https://doi.org/10.1016/1010-7940(91)90 210-b PMID: 2025438

[20] den Bakker MA, Marx A, Mukai K, Ströbel P. Mesenchymal tumours of the mediastinum – part I. Virchows Arch, 2015, 467(5):487–500. https://doi.org/10.1007/s00428-015-1830-8 PMID: 26358059 PMCID: PMC4656709

[21] Alizadeh M, Vafaie M, Tarlan S, Moeini H, Chelkassri FM, Khoeiniha MH, Fathi SM, Didban A, Chegini V. Thymolipoma associated with lymphocytosis in a 6-year-old girl: a case report. Respir Med Case Rep, 2020, 31:101312. https://doi.org/10.1016/j.rmcr.2020.101312 PMID: 33335830 PMCID: PMC7734305

[22] Kitano Y, Yokomori K, Ohkura M, Kataoka T, Narita M, Takemura T. Giant thymolipoma in a child. J Pediatr Surg, 1993, 28(12):1622–1625. https://doi.org/10.1016/0022-3468 (93)90121-z PMID: 8301514

[23] Ganesh Y, Yadala V, Nalini Y, Dal A, Raju AD. Huge mediastinal mass with minimal symptoms: thymolipoma. BMJ Case Rep, 2011, 2011:bcr0520102984. https://doi.org/10.1136/bcr.05. 2010.2984 PMID: 22699472 PMCID: PMC3070336

[24] Amalinei C, Grigoras A, Riscanu LA, Giusca S, Iov T. Peri-cardic thymolipoma – case report. 33rd European Congress of Pathology – Abstracts, Autopsy Pathology E-Posters (E-PS-01), Virchows Arch, 2021, 479(Suppl 1):S180 (E-PS-01-001). https://doi.org/10.1007/s00428-021-03157-8 https://link.springer.com/journal/428/volumes-and-issues/479-1/supplement

[25] Perna V, Morera R, Ramos R, Macia I, Moya J. Giant thymo-lipoma in association with a high production of carbohydrate antigen 19-9 and an increased acetylcholine antibody titer. J Thorac Cardiovasc Surg, 2006, 131(6):1412–1413. https://doi.org/10.1016/j.jtcvs.2006.01.030 PMID: 16733187

[26] Maekawa S, Okabayashi K, Hiratsuka M, Hamada M, Shira-kusa T. Thymolipoma with high production of carbohydrate antigen 19-9. J Thorac Cardiovasc Surg, 2004, 127(6):1845–1847. https://doi.org/10.1016/j.jtcvs.2004.01.022 PMID: 15173759

[27] Moran CA, Rosado-de-Christenson M, Suster S. Thymolipoma: clinicopathologic review of 33 cases. Mod Pathol, 1995, 8(7): 741–744. PMID: 8539231

[28] Sinakos E, Papalavrentios L, Chourmouzi D, Dimopoulou D, Drevelegas A, Akriviadis E. The clinical presentation of Von Meyenburg complexes. Hippokratia, 2011, 15(2):170–173. PMID: 22110302 PMCID: PMC3209683

[29] Paclík A, Dytrych P, Hoskovec D, Jakša R, Krška Z. [Hamartoma of the abdominal cavity and retroperitoneum – a review and a case report]. Rozhl Chir, 2017, 96(9):375–382. PMID: 29063771

[30] Wang T, Liu Y. Outcomes of surgical treatments of pulmonary hamartoma. J Cancer Res Ther, 2016, 12(Suppl):116–119. https://doi.org/10.4103/0973-1482.191620 PMID: 27721267

[31] De Cicco C, Bellomi M, Bartolomei M, Carbone G, Pelosi G, Veronesi G, De Pas T, Spaggiari L, Paganelli G. Imaging of lung hamartomas by multidetector computed tomography and positron emission tomography. Ann Thorac Surg, 2008, 86(6): 1769–1772. https://doi.org/10.1016/j.athoracsur.2008.08.033 PMID: 19021972

[32] Hill LRS, Duis J, Kulungowski AM, Annam A, Siegele B, Nakano TA. A challenging diagnosis: PTEN hamartoma tumor syndrome presenting as isolated soft-tissue vascular anomalies. J Vasc Anom, 2021, 2(2):e011. https://doi.org/10.1097/JOVA. 0000000000000011 https://journals.lww.com/jova/Fulltext/2021/ 06000/A_Challenging_Diagnosis__PTEN_Hamartoma_Tumor. 3.aspx

[33] Hendriks YMC, Verhallen JTCM, van der Smagt JJ, Kant SG, Hilhorst Y, Hoefsloot L, Hansson KBM, van der Straaten PJC, Boutkan H, Breuning MH, Vasen HFA, Bröcker-Vriends AHJT. Bannayan–Riley–Ruvalcaba syndrome: further delineation of the phenotype and management of PTEN mutation-positive cases. Fam Cancer, 2003, 2(2):79–85. https://doi.org/10.1023/ a:1025713815924 PMID: 14574156

[34] Toyama T, Mizuno T, Masaoka A, Shibata K, Yamakawa Y, Niwa H, Torii K. Pathogenesis of thymolipoma: report of three cases. Surg Today, 1995, 25(1):86–88. https://doi.org/10.1007/ BF00309395 PMID: 7749298

[35] Nasseri F, Eftekhari F. Clinical and radiologic review of the normal and abnormal thymus: pearls and pitfalls. Radiographics, 2010, 30(2):413–428. https://doi.org/10.1148/rg.302095131 PMID: 20228326

[36] Goldstein AJ, Oliva I, Honarpisheh H, Rubinowitz A. A tour of the thymus: a review of thymic lesions with radiologic and pathologic correlation. Can Assoc Radiol J, 2015, 66(1):5–15. https://doi.org/10.1016/j.carj.2013.09.003 PMID: 24736228

[37] Guleria P, Jain D. Thymic lesions of the paediatric age group: a comprehensive review of non-neoplastic and neoplastic etiologies. Mediastinum, 2019, 3:24. https://doi.org/10.21037/ med.2019.05.04 PMID: 35118252 PMCID: PMC8794310

[38] Le Marc'hadour F, Pinel N, Pasquier B, Dieny A, Stoebner P, Couderc P. Thymolipoma in association with myasthenia gravis. Am J Surg Pathol, 1991, 15(8):802–809. https://doi.org/10. 1097/00000478-199108000-00012 PMID: 2069215

[39] Bartuma H, Hallor KH, Panagopoulos I, Collin A, Rydholm A, Gustafson P, Bauer HCF, Brosjö O, Domanski HA, Mandahl N, Mertens F. Assessment of the clinical and molecular impact of different cytogenetic subgroups in a series of 272 lipomas with abnormal karyotype. Genes Chromosomes Cancer, 2007, 46(6): 594–606. https://doi.org/10.1002/gcc.20445 PMID: 17370328

[40] Damadoglu E, Salturk C, Takir HB, Ertugrul M, Yilmaz A, Atasalihi A, Yilmaz A. Mediastinal thymolipoma: an analysis of 10 cases. Respirology, 2007, 12(6):924–927. https://doi.org/ 10.1111/j.1440-1843.2007.01150.x PMID: 17986126

[41] Gupta R, Verma S, Bansal K, Mohta A. Thymolipoma in child: a case diagnosed by correlation of ultrasound-guided fine needle aspiration (EUS–FNA) cytology and computed tomography with histological confirmation. Cytopathology, 2014, 25(4):278–279. https://doi.org/10.1111/cyt.12087 PMID: 23902624

[42] Patel RV, Evans K, Sau I, Huddart S. Paediatric giant cervico-mediastinal thymolipoma. BMJ Case Rep, 2014, 2014:bcr 2014203585. https://doi.org/10.1136/bcr-2014-203585 PMID: 24849642 PMCID: PMC4039914

[43] Obeso Carillo GA, García Fontán EM, Cañizares Carretero MÁ. Giant thymolipoma: case report of an unusual mediastinal tumor. Arch Bronconeumol, 2014, 50(12):557–559. https://doi.org/ 10.1016/j.arbres.2013.11.028 PMID: 24985048

[44] Niranjan J, Santosh KV, Indira N, Prakash CJ. Giant cellular thymolipoma: a case report. J Clin Biomed Sci, 2015, 5(1): 37–38. http://www.jcbsonline.ac.in/Articles/Volume5_Issue1/ 10.Case%20Report.pdf http://www.jcbsonline.ac.in/Vol5Issue1. php

[45] Onoda T, Meguro T, Kanno M, Ohta H, Nakamura M, Ohtake H, Mitsui T. Giant thymolipoma in a young child initially diagnosed as cardiomegaly. Pediatr Int, 2015, 57(5):1051–1052. https:// doi.org/10.1111/ped.12786 PMID: 26508197

[46] Othman SA, AlFrayyan OY, AlGhamdi ZM, Makhdom F, AlJehani Y, Elbawab HY, El-Shawarby M. Thymolipoma association with myasthenia gravis: case report. Am J Case Rep, 2020, 21:e923989. https://doi.org/10.12659/AJCR.923 989 PMID: 32745075 PMCID: PMC7423170

[47] Lerro A, De Luca G. Giant thymolipoma causing cardiocompressive syndrome with chronic heart failure. Ann Thorac Surg, 2009, 87(2):644. https://doi.org/10.1016/j.athoracsur.2008.05.060 PMID: 19161808

[48] Rieker RJ, Schirmacher P, Schnabel PA, Moser K, Hoffmann H, Dienemann H, Pfannschmidt J. Thymolipoma. A report of nine cases, with emphasis on its association with *myasthenia gravis*. Surg Today, 2010, 40(2):132–136. https://doi.org/10.1007/s00595-009-4042-5 PMID: 20107952

[49] Meriggioli MN, Sanders DB. Muscle autoantibodies in *myasthenia gravis*: beyond diagnosis? Expert Rev Clin Immunol, 2012, 8(5):427–438. https://doi.org/10.1586/eci.12.34 PMID: 22882218 PMCID: PMC3505488

[50] Poursadeghfard M, Abolhasani Foroughi A, Karamimagham S. Thymolipoma-associated *myasthenia gravis* with high titer of anti-MuSKAb: a case report. Int J Mol Cell Med, 2019, 8(1):90–93. https://doi.org/10.22088/IJMCM.BUMS.8.1.90 PMID: 32195208 PMCID: PMC7073264

[51] Guimarães MD, Benveniste MFK, Bitencourt AGV, Andrade VP, Souza LP, Gross JL, Godoy MCB. Thymoma originating in a giant thymolipoma: a rare intrathoracic lesion. Ann Thorac Surg, 2013, 96(3):1083–1085. https://doi.org/10.1016/j.athoracsur.2013.01.031 PMID: 23992709

[52] Yvorel V, Forest F, Parietti E, Karpathiou G, Stachowicz ML, Patoir A, Tiffet O, Péoc'h M. B3 thymoma arising within thymolipoma. Pathology, 2015, 47(7):702–705. https://doi.org/10.1097/PAT.0000000000000335 PMID: 26517631

[53] Breek JK, Vallaeys JH, Rutsaert RR. Simultaneous presentation of a thyrolipoma and a thymolipoma in a young man. Eur J Surg, 1997, 163(12):941–943. PMID: 9449448

[54] Mangiameli G, Bekmezian N, Hernigou A, Le Pimpec-Barthes F. Exceptional thyrolipoma and thymolipoma association: is there a syndrome? Interact Cardiovasc Thorac Surg, 2021, 32(5):828–830. https://doi.org/10.1093/icvts/ivaa332 PMID: 33373999 PMCID: PMC8691556

[55] Trites AE. Thyrolipoma, thymolipoma and pharyngeal lipoma: a syndrome. Can Med Assoc J, 1966, 95(24):1254–1259. PMID: 5954492 PMCID: PMC1935725

[56] Mohapatra CKR, Jadhav RB, Mulla AM, Khandekar JV, Ammannaya GK. An unusual case of thymolipoma as an anterior mediastinal mass in a 17-year-old girl – case report. Indian J Thorac Cardiovasc Surg, 2016, 32(2):146–148. https://doi.org/10.1007/s12055-016-0420-y https://link.springer.com/article/10.1007/s12055-016-0420-y

[57] Vaziri M, Rad K. Progressive dyspnea in a 40-year-old man caused by giant mediastinal thymolipoma. Case Rep Surg, 2016, 2016:3469395. https://doi.org/10.1155/2016/3469395 PMID: 27293949 PMCID: PMC4886086

[58] Yusuf Mohamud MF, Ahmed MA, Ali IH. Extensive mediastinal thymolipoma mimicking pulmonary edema. J Surg Case Rep, 2020, 2020(4):rjaa080. https://doi.org/10.1093/jscr/rjaa080 PMID: 32368336 PMCID: PMC7190029

[59] Restrepo CS, Pandit M, Rojas IC, Villamil MA, Gordillo H, Lemos D, Mastrogiovanni L, Diethelm L. Imaging findings of expansile lesions of the thymus. Curr Probl Diagn Radiol, 2005, 34(1):22–34. https://doi.org/10.1067/j.cpradiol.2004.10.001 PMID: 15644860

[60] Romero-Guadarrama MB, Durán-Padilla MA, Cruz-Ortíz H, Castro-Gómez L, López-Vancell D, Novelo-Retana V, Santiago-Prieto AC, Fierro-Chávez E, Rodríguez-Martínez HA. Diagnosis of thymolipoma with fine needle aspiration biopsy. Report of a case initially misdiagnosed as liposarcoma. Acta Cytol, 2004, 48(3):441–446. https://doi.org/10.1159/000326401 PMID: 15192967

[61] Zou D, Luo H, Feng Y, Zeng B, Lei Y. Massive thymic hyperplasia in an adult: a rare case report and literature review. Int J Surg Case Rep, 2018, 47:104–108. https://doi.org/10.1016/j.ijscr.2018.04.037 PMID: 29754034 PMCID: PMC5994738

[62] Juanpere S, Cañete N, Ortuño P, Martínez S, Sanchez G, Bernado L. A diagnostic approach to the mediastinal masses. Insights Imaging, 2013, 4(1):29–52. https://doi.org/10.1007/s13244-012-0201-0 PMID: 23225215 PMCID: PMC3579993

[63] Azizad S, Sannananja B, Restrepo CS. Solid tumors of the mediastinum in adults. Semin Ultrasound CT MR, 2016, 37(3):196–211. https://doi.org/10.1053/j.sult.2016.03.002 PMID: 27261345

[64] Mohan Rao PS, Moorthy N, Shankarappa RK, Bhat P, Nanjappa MC. Giant mediastinal thymolipoma simulating cardiomegaly. J Cardiol, 2009, 54(2):326–329. https://doi.org/10.1016/j.jjcc.2008.12.008 PMID: 19782275

[65] Kim YK, Shin N, Park WY, Park DY, Huh GY, Lee CH. Mediastinal thymolipoma with striated myoid cells: report of a peculiar case. Korean J Pathol, 2013, 47(6):596–598. https://doi.org/10.4132/KoreanJPathol.2013.47.6.596 PMID: 24421857 PMCID: PMC3887166

[66] Moran CA, Zeren H, Koss MN. Thymofibrolipoma. A histologic variant of thymolipoma. Arch Pathol Lab Med, 1994, 118(3):281–282. PMID: 8135632

[67] Kang GH, Han J, Kim TS, Choi YS, Um SW. Thymofibrolipoma: a brief case report. Korean J Pathol, 2010, 44(3):338–340. https://doi.org/10.4132/KoreanJPathol.2010.44.3.338 https://www.jpatholtm.org/journal/view.php?doi=10.4132/KoreanJPathol.2010.44.3.338

[68] Ogino S, Franks TJ, Deubner H, Koss MN. Thymohemangiolipoma, a rare histologic variant of thymolipoma: a case report and review of the literature. Ann Diagn Pathol, 2000, 4(4):236–239. https://doi.org/10.1053/adpa.2000.8131 PMID: 10982301

[69] Jetley NK, Al-Assiri AH, Al-Helal AS, Al-Bin Ali AM. Down's syndrome as a factor in the diagnosis, management, and outcome in patients of Morgagni hernia. J Pediatr Surg, 2011, 46(4):636–639. https://doi.org/10.1016/j.jpedsurg.2010.10.001 PMID: 21496530

[70] Sharma K, Sharma S, Seth R, Gupta DK. Giant bilateral pediatric thymolipoma presenting with respiratory distress. J Pediatr Surg Case Rep, 2021, 69:101849. https://doi.org/10.1016/j.epsc.2021.101849 https://www.sciencedirect.com/science/article/pii/S2213576621000713?via%3Dihub

[71] Knight CS, Cerfolio RJ, Winokur TS. Angiomyolipoma of the anterior mediastinum. Ann Diagn Pathol, 2008, 12(4):293–295. https://doi.org/10.1016/j.anndiagpath.2006.12.007 PMID: 18620999

[72] Panagopoulos I, Gorunova L, Agostini A, Lobmaier I, Bjerkehagen B, Heim S. Fusion of the *HMGA2* and *C9orf92* genes in myolipoma with t(9;12)(p22;q14). Diagn Pathol, 2016, 11:22. https://doi.org/10.1186/s13000-016-0472-8 PMID: 26857357 PMCID: PMC4746792

[73] Kammerer-Jacquet SF, Thierry S, Cabillic F, Lannes M, Burtin F, Henno S, Dugay F, Bouzillé G, Rioux-Leclercq N, Belaud-Rotureau MA, Stock N. Differential diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma: utility of p16 in combination with MDM2 and CDK4 immunohistochemistry. Hum Pathol, 2017, 59:34–40. https://doi.org/10.1016/j.humpath.2016.08.009 PMID: 27597521

[74] Chrisinger JSA. Update on lipomatous tumors with emphasis on emerging entities, unusual anatomic sites, and variant histologic patterns. Surg Pathol Clin, 2019, 12(1):21–33. https://doi.org/10.1016/j.path.2018.11.001 PMID: 30709444

[75] Puttarajappa C, Dhoble A. Mediastinal lipomatosis as a cause of low voltage complexes on electrocardiogram and widened mediastinum: a case report. Cases J, 2008, 1(1):171. https://doi.org/10.1186/1757-1626-1-171 PMID: 18803846 PMCID: PMC2556664

[76] Dubashi B, Cyriac S, Tenali SG. Clinicopathological analysis and outcome of primary mediastinal malignancies – a report of 91 cases from a single institute. Ann Thorac Med, 2009, 4(3):140–142. https://doi.org/10.4103/1817-1737.53354 PMID: 19641646 PMCID: PMC2714569

[77] Wu M, Sun K, Gil J, Gan L, Burstein DE. Immunohistochemical detection of p63 and XIAP in thymic hyperplasia and thymomas. Am J Clin Pathol, 2009, 131(5):689–693. https://doi.org/10.1309/AJCPVTZ06DHKCOGP PMID: 19369629

[78] Radovich M, Pickering CR, Felau I, Ha G, Zhang H, Jo H, Hoadley KA, Anur P, Zhang J, McLellan M, Bowlby R, Matthew T, Danilova L, Hegde AM, Kim J, Leiserson MDM, Sethi G, Lu C, Ryan M, Su X, Cherniack AD, Robertson G, Akbani R, Spellman P, Weinstein JN, Hayes DN, Raphael B, Lichtenberg T, Leraas K, Zenklusen JC; Cancer Genome Atlas Network, Fujimoto J, Scapulatempo-Neto C, Moreira AL, Hwang D, Huang J, Marino M, Korst R, Giaccone G, Gokmen-Polar Y, Badve S, Rajan A, Ströbel P, Girard N, Tsao MS, Marx A, Tsao AS, Loehrer PJ. The integrated genomic landscape of thymic epithelial tumors. Cancer Cell, 2018, 33(2):244–258.e10. https://doi.org/10.1016/j.ccell.2018.01.003 PMID: 29438696 PMCID: PMC5994906

[79] Liu PP, Su YC, Niu Y, Shi YF, Luo J, Zhong DR. Comparative clinicopathological and immunohistochemical study of micro-nodular thymoma and micronodular thymic carcinoma with lymphoid stroma. J Clin Pathol, 2021, Sep 7, jclinpath-2021-207819. https://doi.org/10.1136/jclinpath-2021-207819 PMID: 34493600

[80] Argani P, de Chiocca IC, Rosai J. Thymoma arising with a thymolipoma. Histopathology, 1998, 32(6):573–574. PMID: 9675602

[81] Kaplan T, Han S, Han U, Atac GK, Yanik S. Thymoma type B1 arising in a giant supradiaphragmatic thymolipoma. Asian Cardiovasc Thorac Ann, 2014, 22(9):1109–1111. https://doi.org/10.1177/0218492313504576 PMID: 24887884

[82] Haddad H, Joudeh A, El-Taani H, Mansour A, Morcos B, Fayoumi S, Sughayer M. Thymoma and thymic carcinoma arising in a thymolipoma: report of a unique case. Int J Surg Pathol, 2009, 17(1):55–59. https://doi.org/10.1177/1066896908315822 PMID: 18480395

[83] Conyers R, Young S, Thomas DM. Liposarcoma: molecular genetics and therapeutics. Sarcoma, 2011, 2011:483154. https://doi.org/10.1155/2011/483154 PMID: 21253554 PMCID: PMC3021868

[84] Kim HJ, Kim HK, Park G, Min SK, Cha HJ, Lee H, Choi SJ, Na HY, Choe JY, Kim JE. Comparative pathologic analysis of mediastinal B-cell lymphomas: selective expression of p63 but no GATA3 optimally differentiates primary mediastinal large B-cell lymphoma from classic Hodgkin lymphoma. Diagn Pathol, 2019, 14(1):133. https://doi.org/10.1186/s13000-019-0918-x PMID: 31831043 PMCID: PMC6909622

[85] Fakhri B, Ai W. Current and emerging treatment options in primary mediastinal B-cell lymphoma. Ther Adv Hematol, 2021, 12:20406207211048959. https://doi.org/10.1177/20406207211048959 PMID: 34659697 PMCID: PMC8511915

[86] Hishima T, Fukayama M, Hayashi Y, Fujii T, Ooba T, Funata N, Koike M. CD70 expression in thymic carcinoma. Am J Surg Pathol, 2000, 24(5):742–746. https://doi.org/10.1097/00000478-200005000-00014 PMID: 10800994

[87] Enkner F, Pichlhöfer B, Zaharie AT, Krunic M, Holper TM, Janik S, Moser B, Schlangen K, Neudert B, Walter K, Migschitz B, Müllauer L. Molecular profiling of thymoma and thymic carcinoma: genetic differences and potential novel therapeutic targets. Pathol Oncol Res, 2017, 23(3):551–564. https://doi.org/10.1007/s12253-016-0144-8 PMID: 27844328 PMCID: PMC5487866

[88] Schmoke N, Derderian SC, Partrick DA. Thoracoscopic resection of giant thymolipoma. J Pediatr Surg Case Rep, 2020, 63: 101669. https://doi.org/10.1016/j.epsc.2020.101669 https://www.sciencedirect.com/science/article/pii/S2213576620303031?via%3Dihub

Corresponding authors

Raluca Anca Balan, Associate Professor, MD, PhD, Department of Morphofunctional Sciences I, Grigore T. Popa University of Medicine and Pharmacy, 16 University Street, 700115 Iaşi, Romania; Phone +40720–550 530, e-mail: raluca.balan@umfiasi.ro

Adriana Grigoraş, Associate Professor, MD, PhD, Department of Morphofunctional Sciences I, Grigore T. Popa University of Medicine and Pharmacy, 16 University Street, 700115 Iaşi, Romania; Phone +40740–170 027, e-mail: adriana.grigoras@umfiasi.ro