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CASE REPORT

Aspects of thymic pathologies in paediatric patients. Case study of true thymic hyperplasia and the diagnostic approach

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ABSTRACT

Proliferative lesions of the thymus are very rare in children and represent about 2% of mediastinal tumours. They may result from organ hyperplasia, the presence of cysts, or germinal and epithelial neoplasms. All of them can result in massive enlargement of thymus but differ considerably in terms of course and prognosis. This article presents the case of a 2.5-year-old girl with symptoms of respiratory tract infection not responding to antibiotics and with an enlarged thymus, which transpired to be true thymic hyperplasia. In this example, the details of the multidisciplinary diagnostic approach, differentiation, and treatment modalities in children were discussed. An algorithm of the proceedings, with respect to the child's age, was proposed. Although the described pathologies are casuistic in nature, they indicate a necessity to increase vigilance towards symptoms that persist over a prolonged time with no response to standard treatment, because early diagnosis allows the application of appropriate treatment in advance.

KEY WORDS:
children, mediastinal tumour, true thymic hyperplasia, widened mediastinum.

INTRODUCTION

The thymus, which is located within the anterior mediastinum, plays the role of the primary (central) lymphoid organ of the immune system, responsible for the controlled maturation of T-cells. During one's lifetime the thymus undergoes substantial morphological changes reaching its largest size during puberty (Figure 1), then involution of the gland begins and continues with advancing age, being gradually replaced by adipose tissue [2].

Proliferative lesions of the thymus are very rare in children and represent only 2% of all mediastinal tumours in paediatric patients. An enlarged thymus may occur due to thymic hyperplasia, congenital or acquired cysts, epithelial neoplasms – thymolipoma, thymoma, carcinoma, or thymic neuroendocrine tumour (carcinoid) [3]. Among all anterior mediastinum tumours in neonates and infants, germ cell tumours (especially teratomas), congenital cysts, and thymic hyperplasia are most common. Teratomas, yolk sac tumours, and cysts are predominant in pre-schoolers. In children over 5 years of age, the most common type of anterior mediastinum tumours are lymphomas, while thymomas and thymic carcinomas are rarely observed. Sarcomas, although very rare, must be included in differential diagnosis in all paediatric patients [4].

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CASE REPORT

A 2.5-year-old girl was admitted to hospital due to pneumonia treatment failure in an outpatient setting. Her history included productive cough for 2 weeks, without fever; and persistent asymmetry in lung auscultation with the negation of foreign body aspiration.

On admission, she presented with symptoms of nasopharyngitis, dullness over the whole right lung in percussion, and bronchial sound over the right upper lobe in auscultation. Blood tests revealed leucocytosis, lymphocytosis (Table 1), and low levels of C-reactive protein. In a chest X-ray massive inflammatory and atelectasis lesions were described within the mid and inferior right lobes without mediastinal shift and pleural effusion (Figure 2A). Antibiotic treatment (ceftriaxone, clarithromycin) was introduced, without lung improvement; hence, further diagnostic steps were performed. In flexible bronchoscopy there was evidence of purulent bronchitis and bronchomalacia within the middle lobe, with negative results of microbial culture tests of bronchoalveolar lavage fluid. Humoral, and in further follow-up also cellular, immune deficiencies were ruled out (Table 1). A follow-up chest X-ray was performed (Figure 2B) together with chest computed tomography (CT), which showed a massive, heterogeneous in composition, tumour lesion localised within the right anterosuperior mediastinum, reaching the right supradiaphragmatic area with consolidation/atelectasis of the right lung and some pleural effusion at this side, without enlargement of the chest lymph nodes (Figure 2C, D, E, F). Because CT scan morphology raised suspicions of an immature teratoma, blood tests for tumour/carcinoma markers were

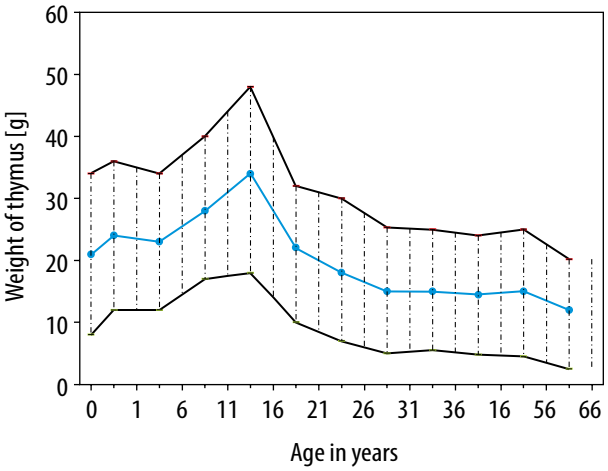

FIGURE 1. Graph depicting the relationship between mean thymus mass and age [1]

TABLE 1. Results of immunological and serological tests performed during hospitalisation, one month after surgery and 6 months after surgery

Parameters	Hospitalisation	One month	Six months	Normal
IgG [g/l]	9.11	7.65	–	4.57–11.90
IgA [g/l]	0.51	0.45	–	0.22–1.22
IgM [g/l]	1.18	1.34	–	0.36–1.77
IgE [IU/ml]	–	< 4.56	–	0.00–60.00
C3c [g/l]	–	1.15	1.16	0.90–1.80
C4 [g/l]	–	0.12	0.14	0.13–0.40
Chemiluminescence[a]	–	Normal	–	Normal
Autoantibodies in serum	–	Absent	–	Absent
Anti-HBs [IU/l]	–	> 1000	–	> 10
Anti-rubella IgG [IU/ml]	–	154	–	Positive
Anti-tetanus toxoid [IU/ml]	–	> 5.0	–	> 5.0
Anti-CMV	–	–	IgG (–); IgM (–)	
WBC [1/µl]	21450	15,670	8670	4860–13380
Lymphocytes [1/µl]	1320	9731	5100	1130–5700
T-cells				
CD3 [1/µl]	–	8174	3047	1400–3700
CD4 [1/µl]	–	5255	1596	700–2200
CD8 [1/µl]	–	1849	1112	490–1300
CD3/HLA-DR [1/µl]	–	341	256	115–215
B-cells				
CD19 [1/µl]	–	535	1257	390–1400
NK-cells (CD3-16+56+) [1/µl]	–	973	435	130–720

[a]*Response to stimulation with latex*

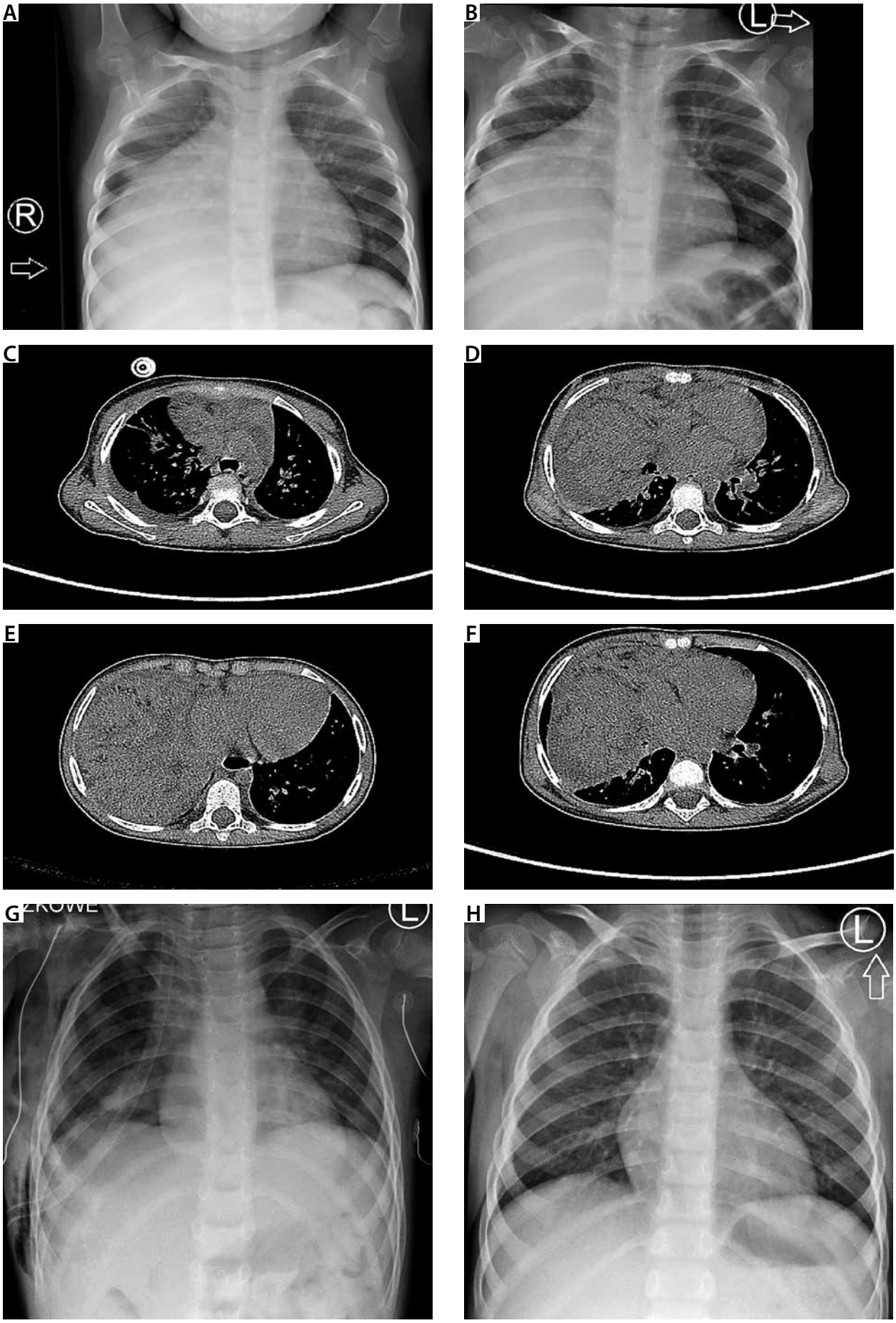

FIGURE 2. Image **A**) Chest X-ray performed upon admission. **B**) Chest X-ray performed on the ninth day of hospitalisation. **C**– **F**) Chest CT. **G**) Chest X-ray performed after surgery. **H**) Chest X-ray performed several months after surgery

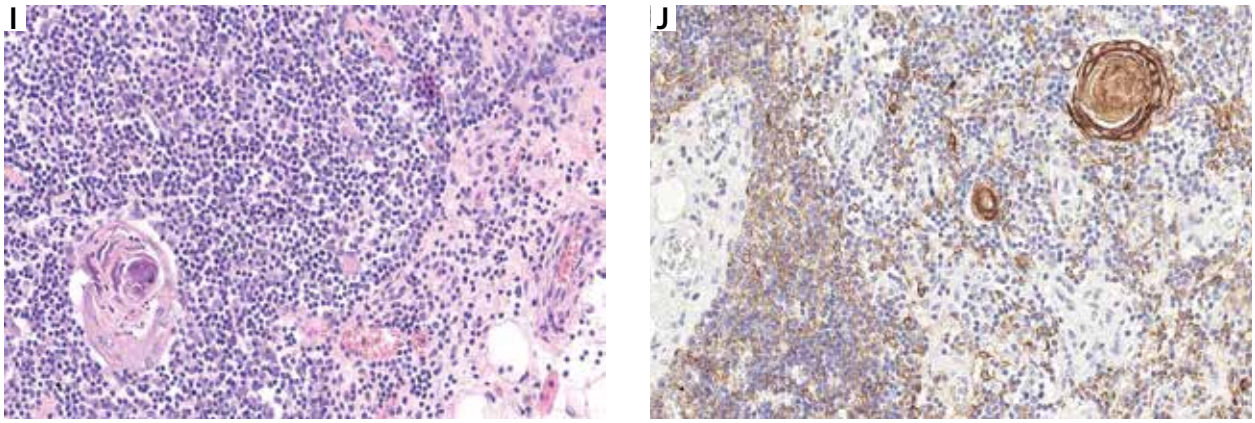

FIGURE 2. Cont. I) Histological evaluation – routine staining with haematoxylin and eosin. Image J) Histological evaluation – CK staining – cytokeratin AE1/AE3 (staining of thymic epithelial cells and Hassall's corpuscles)

done, with negative results (Table 2). Computed tomography scans of the head, abdomen, and pelvis showed no pathologies.

On the 21st day of hospitalisation the patient was qualified for an ultrasound-guided core biopsy of the tumour, performed through the intercostal space. The intraoperative histopathological examination of the frozen biopsy specimen revealed a benign lesion originating from the thymus. In the next step during the same procedure, right-sided thoracotomy was performed, and 2 lesions (first 15.5 × 9 × 5 cm mass of 315 g, and second 3.5 × 1.5 × 0.8 cm mass of 3.2 g) were totally resected. The tumour was located in the anterior mediastinum, adjacent to lung parenchyma, pericardium, and right dome of the diaphragm with its top reaching the superior vena cava. The right phrenic nerve adjacent to the tumour was preserved without damage. After removal of the tumour, the right lung expanded properly. The tumour mass equalled 2.58% of the girl's body weight. Histopathological examination (Figure 2I, J) confirmed morphology consistent with a hyperplastic thymus. The patient was discharged home on the seventh day after the surgery. In further follow-up the clinical course was uneventful without tumour recurrence in chest control evaluation (Figure 2G, H) and in the blood testing after one and 6 months since the intervention (Table 1). One year after this operation she presents with no medical problems, subjective complaints, no infections, and good tolerance of physical activities.

TABLE 2. RESULTS of additional tests performed during hospitalisation

Parameters	Value	Normal
α-fetoprotein [ng/ml]	4	< 10.0
β-hCG [mIU/ml]	< 2.0	< 10.0
Neuron-specific enolase [ng/ml]	25.35	< 16.30
3-methoxytyramine in 24-hr UCa [µg/mg of creatinine]	2.16	0.14–0.49
Homovanillic acid in 24-hr UCa [µg/mg of creatinine]	30.1	0.0–22.0

[a]24-hour
UC – 24-hour urine collection

DISCUSSION

True thymic hyperplasia (TTH) is a diffuse organ over-enlargement in relation to the age-specific size and mass with normal thymic microscopic architecture. True thymic hyperplasia is typically observed in 3 clinical conditions:

- without any associated disorders,
- enlargement caused by a rebound effect in regeneration process after steroid therapy, cancer treatment, thermal burns, or tuberculosis,
- association with endocrine disorders (thyrotoxicosis, Addison's disease, acromegaly, aplasia of the pituitary gland), sarcoidosis, or Beckwith-Wiedemann syndrome [5].

The clinical case presented above involved a very rare example of the first clinical condition.

EPIDEMIOLOGY AND AETIOLOGY

Incidence and prevalence rates of TTH are not known, but most often it occurs in neonates and in young children, unlike thymomas, thymic carcinomas, and lymphoid follicular hyperplasia, being mostly identified in adolescents and adults. The aetiology and pathogenesis of TTH are still not clear [4].

SYMPTOMS AND DIAGNOSTICS

True thymic hyperplasia very rarely causes clinical symptoms. Most often, disease is identified incidentally in follow-up medical imaging. However, massive TTH may cause compression of surrounding structures (mass effect – with atelectasis, acute or recurrent respiratory tract infections, cough, dysphagia and aspiration, discomfort in the chest) and even life-threatening conditions (respiratory and/or circulatory failure, haemorrhagic shock as the result of haemorrhage from the thymus) [4, 6, 7]. In

TABLE 3. FREQUENCY of clinical manifestations of massive thymic hyperplasia in paediatric patients at the time of hospital admission [7]

Feature	Frequency (%)
Asymptomatic	38
Cough	38
Respiratory tract infections	35
Respiratory failure	29
Peripheral lymphocytosis	29
Airway obstruction	6
Dysphagia	3
Discomfort in chest	3
Splenomegaly	3

symptomatic children cough, respiratory tract infection, or respiratory insufficiency are the leading clinical presentations (Table 3).

Blood tests in some cases show lymphocytosis – normalised in the postoperative period, while humoral and cell-mediated immunity markers remain within normal range [8].

There are no pathognomonic features specific to TTH. A chest X-ray shows the widening of the anterior mediastinal shadow, absence of calcifications, in some cases the thymic sail sign or wave sign, and – depending on the extent of organ enlargement – features consistent with lung parenchyma and great vessel compression, mediastinal shift, or pleural effusion. In chest CT, TTH presents with a homogeneous and diffuse appearance with symmetrical enlargement in most cases with adipose tissue in their composition [9].

Histopathology reveals normal thymic structure with normal lobular architecture. Immunohistochemical tests show no deviations from a normal thymus and present normal cellular response to growth stimulation with interleukins [8]. However, some authors described a quantitative decrease of mature T-cells in the cortical and medullary components of the thymus with accumulation of immature forms of T-cells [10].

DIAGNOSTIC CRITERIA

True thymic hyperplasia is defined as organ enlargement in relation to the age-specific size and mass of the thymus with normal microscopic architecture. Figure 1 and Table 4 show the relationship between mass of the thymus and the patient's age. True thymic hyperplasia can be classified as massive when the following criteria are met: the thymic shadow is larger than the heart shape in chest posterior-anterior X-ray, and the mass of the thymus is several times greater than the normal mass specific to the patient's age and exceeds more than 2% of the patient's body weight [6, 7]. The presented case fulfilled these additional diagnostic criteria.

DIFFERENTIAL DIAGNOSTICS

True thymic hyperplasia should be differentiated from other chest tumours within the anterior mediastinum (thymoma, carcinoid tumour, thymolipoma, Hodgkin's or non-Hodgkin's lymphomas, germ cell tumours) and non-neoplastic diseases (cysts of various aetiologies or diseases accompanied by benign enlargement of the mediastinal lymph nodes, e.g. angiofollicular ganglionic hyperplasia (Castleman's disease]) [2, 3]. The most frequently occurring types of mediastinal lesions grouped by age in the context of a diagnostic approach are presented in the form of an algorithm (Figure 3) [11, 12].

Important factors in differential diagnostics are age, clinical manifestation, as well as the patient's history.

Anterior mediastinum tumours might present with similar clinical symptoms, regardless of pathology. Cases of very rapid expansion of TTH mass require urgent diagnostics for neoplastic pathology. In children with a history of severe stress (thermal burn, surgery, cancer therapies), subsequent "rebound" hyperplasia might be considered in differential diagnosis of enlarged thymus [5].

Recommended laboratory tests include a complete blood count, α-fetoprotein, β-hCG, chromogranin, neuron-specific enolase, lactate dehydrogenase, and uric acid levels. Computed tomography of the chest, and when indicated, also of the abdomen and head, are usually performed, but there are no pathognomonic features differentiating between various thymic pathologies. The decisive tool for definitive diagnosis is histopathological examination in combination with immunohistochemical tests.

TREATMENT

True thymic hyperplasia treatment is controversial (low effectiveness) and depends on the patient's age and clinical symptoms. The conservative approach is based on systemic glucocorticosteroid therapy (prednisone 2 mg/kg) [13]. However, surgical intervention (thymectomy) in children up to one year of age is associated with decreasing circulating T-cells. Therefore, in patients younger than 18 months presenting with confirmed diagnosis, watchful observation is suggested with the introduction of glucocorticosteroid therapy in the course of symptom propagation. In the case of further thymus enlargement or life-treating condition, thymectomy becomes a necessity [6]. However, considering the very few symptoms that accompany TTH, the lack of pathognomonic features in additional examinations, and the much more common occurrence of non-benign anterior mediastinal tumours, the first line of treatment in suspicion of TTH seems to be a complete resection of the thymus and histopathological examination to unequivocally confirm the diagnosis.

CONCLUSIONS

From the presented case, it can be concluded that thymic pathologies have non-specific manifestations; therefore, oncological vigilance should be maintained in the case of chronic and untypical symptoms, especially no response to conventional treatment. We believe that the presented algorithm (Figure 3) could be suitable in the diagnostic approach of middle mediastinal tumours, keeping in mind that history taking is of high importance in suspected cases.

TABLE 4. Mean values and upper limits of normal for thymus mass by age (after resection of perithymic adipose tissue) [4]

Age	Mean mass [g]	Upper limit of normal mass [g]
At birth	12	25
12 months	20	45
7–30 years	25–35	50
40–60 years	10–15	30

DISCLOSURES

1. Jagiellonian University Medical College Research Ethics Committee agreement was obtained (KEBN UJ CM 118.6120.56.2023).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

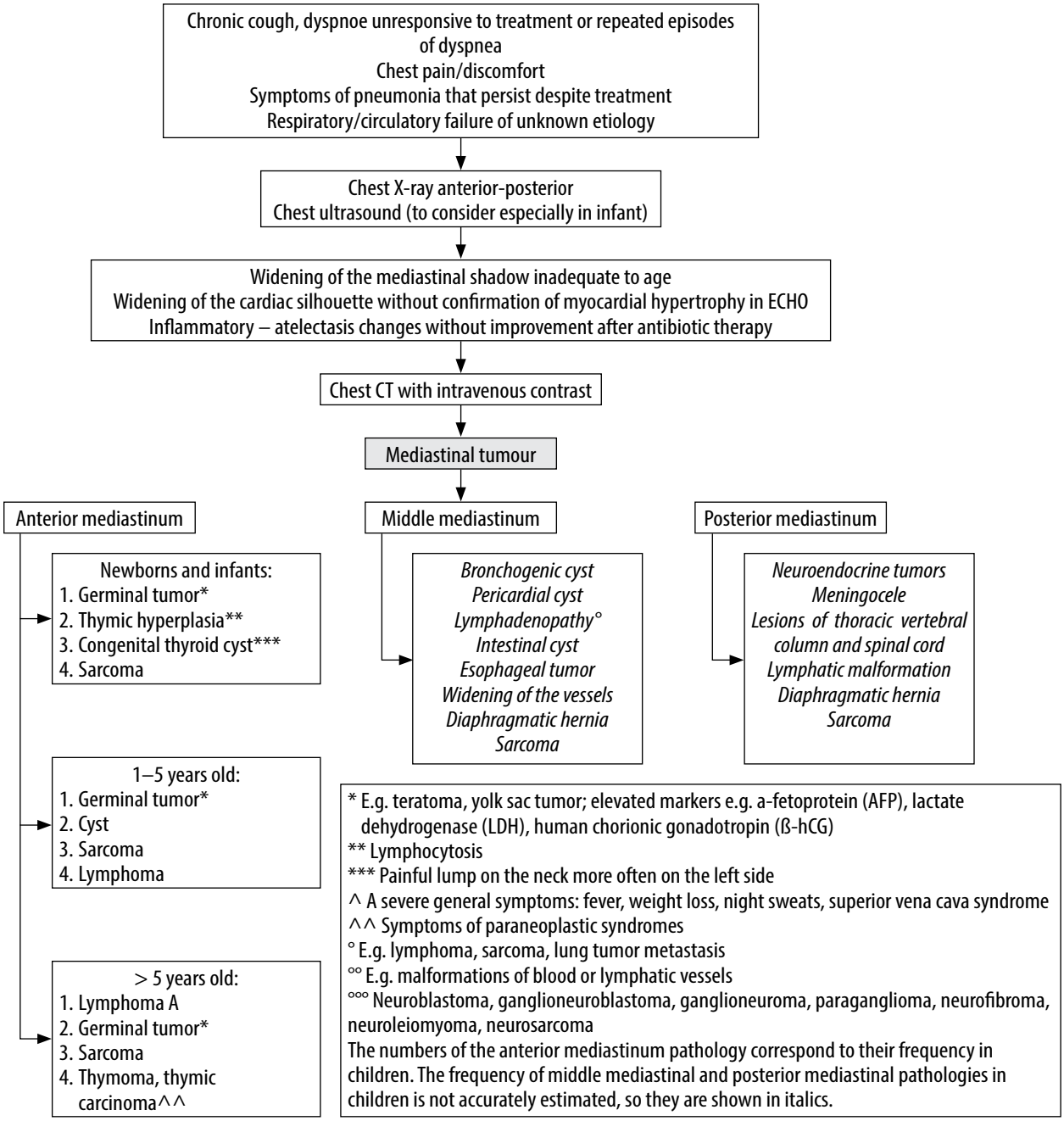

FIGURE 3. Algorithm of the diagnostic approach to mediastinal tumours in children

REFERENCES

1. Lack EE. Thymic hyperplasia with massive enlargement: report of two cases with review of diagnostic criteria. J Thorac Cardiovasc Surg. 1981; 81: 741-746.
2. Sreedher G, Tadros SS, Janitz E. Pediatric mediastinal masses. Pediatr Radiol 2022; 52: 1935-1947.
3. Vo NH, Shashi KK, Winant AJ, et al. Imaging evaluation of the pediatric mediastinum: new International Thymic Malignancy Interest Group classification system for children. Pediatr Radiol 2022; 52: 1948-1962.
4. Weis CA, Märkl B, Schuster T, et al. „Echte Thymushyperplasie": Differenzialdiagnose der Thymusvergrößerung bei Säuglingen und Kindern [True thymic hyperplasia: differential diagnosis of thymic mass lesions in neonates and children]. Pathologe 2017; 38: 286-293.
5. Hofmann WJ, Möller P, Otto HF. Thymic hyperplasia. I. True thymic hyperplasia. Review of the literature. Klin Wochenschr 1987; 65: 49-52.
6. Eifinger F, Ernestus K, Benz-Bohm G, et al. True thymic hyperplasia associated with severe thymic cyst bleeding in a newborn: case report and review of the literature. Ann Diagn Pathol 2007; 11: 358-362.
7. Linegar AG, Odell JA, Fennell WM, et al. Massive thymic hyperplasia. Ann Thorac Surg 1993; 55: 1197-1201.
8. Rice HE, Flake AW, Hori T, et al. Massive thymic hyperplasia: characterization of a rare mediastinal mass. J Pediatr Surg 1994; 29: 1561-564.
9. Ricci C, Pescarmona E, Rendina E.A, et al. True Thymic Hyperplasia: A Clinicopatological Study. Ann Thorac Surg 1989; 47: 741-745.
10. Ruco LP, Rosati S, Palmieri B, et al. True thymic hyperplasia: a histological and immunohistochemical study. Histopatology 1989; 15: 640-643.
11. Taka M, Kobayashi S, Mizutomi K, et al. Diagnostic approach for mediastinal masses with radiopathological correlation. Eur J Radiol. 2023; 162: 110767.
12. Biko DM, Lichtenberger JP 3rd, Rapp JB, et al. Mediastinal Masses in Children: Radiologic-Pathologic Correlation. Radiographics. 2021; 41: 1186-1207
13. Gow KW, Kobrynski L, Abramowsky C, et al. Massive benign thymic hyperplasia in a six month old girl: case report. Am Surg 2003; 69: 717-719.