

# Massive true thymic hyperplasia in a 3-month-old infant: case report and literature review

Min Yang<sup>1\*</sup>, Lin Zeng<sup>2\*</sup>, Yi Ji<sup>1</sup>, Bo Xiang<sup>1</sup>, Zhi-cheng Xu<sup>1</sup>

<sup>1</sup>Department of Pediatric Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan Province, the People's Republic of China; <sup>2</sup>President & Dean's Office, West China Hospital of Sichuan University, Chengdu, Sichuan Province, the People's Republic of China.

## ABSTRACT

**Background.** True thymic hyperplasia (TTH) is characterized as a distinct increase in both size and weight of thymus, which retains normal microscopic and immunohistochemical appearances. Massive true thymic hyperplasia (MTTH) is an extremely rare but significant subtype of TTH in pediatric ages due to its potentially serious consequences. It was reported that the age of cases with MTTH was predominantly between 1 and 15 years, while those before 1 year rarely occurred. By presenting the diagnosis and treatment process of our case as well as reviewing the related literature, we aimed to analyze the clinical characteristics of MTTH for patients younger than 1 year.

**Case.** A 3-month-old male infant was admitted to our department with a chief complaint of gradually increasing polypnea over 9 days, whose preoperative imaging examination showed a large intrathoracic soft tissue shadow predominantly on the right side. The percutaneous fine-needle biopsy guided by ultrasonography was performed to identify its diagnosis. However, proliferating lymphocytes and Hassall's corpuscles were seen microscopically in the biopsy tissues, which were immunohistochemically positive for CD3, CD19, CD20, CD99, TdT, PCK and Ki67 (>90%). Due to the aggravating symptoms, a second operation with total thymectomy was carried out successfully for this infant, which confirmed the diagnosis of TTH again by both morphological study and immunohistochemical staining from the surgical specimen.

**Conclusions.** By reviewing the literature, there were only 10 cases with MTTH reported between 1975 and 2020 for children aged <1 year of life, together with our present one. In MTTH patient's sex had an obviously male predominance (70%). Nine out of 10 presented initial symptoms or signs related to respiratory system and 6 patients showed respiratory distress. All patients were successfully treated by surgical thymectomy without any postoperative complications. The prognosis of MTTH was very successful.

**Key words:** true thymic hyperplasia, massive true thymic hyperplasia, infant, biopsy, thymectomy.

The thymus is an important immune organ for children, whose size and weight decreases with age.<sup>1,2</sup> True thymic hyperplasia (TTH) is characterized as a distinct increase in both size and weight of thymus, which retains normal microscopic and immunohistochemical appearances.<sup>3-5</sup> Massive true thymic hyperplasia (MTTH) is an extremely rare but significant

subtype of TTH in pediatric ages due to its potentially serious consequences, which is rather difficult to be distinguished from anterior mediastinal tumors such as thymic lymphoma and thymoma.<sup>6</sup> MTTH rarely occurs in patients younger than 1 year.<sup>1,2</sup> Here, we report a 3-month-old infant who was clinically diagnosed as MTTH. We also reviewed the clinical features of MTTH for children aged <1 year of life in the literature.

✉ Zhi-cheng Xu  
xzcxcw@163.com

Received 30th August 2020, revised 8th November 2020, accepted 4th December 2020.

\*These authors contribute equally as co-first authors.

## Case Report

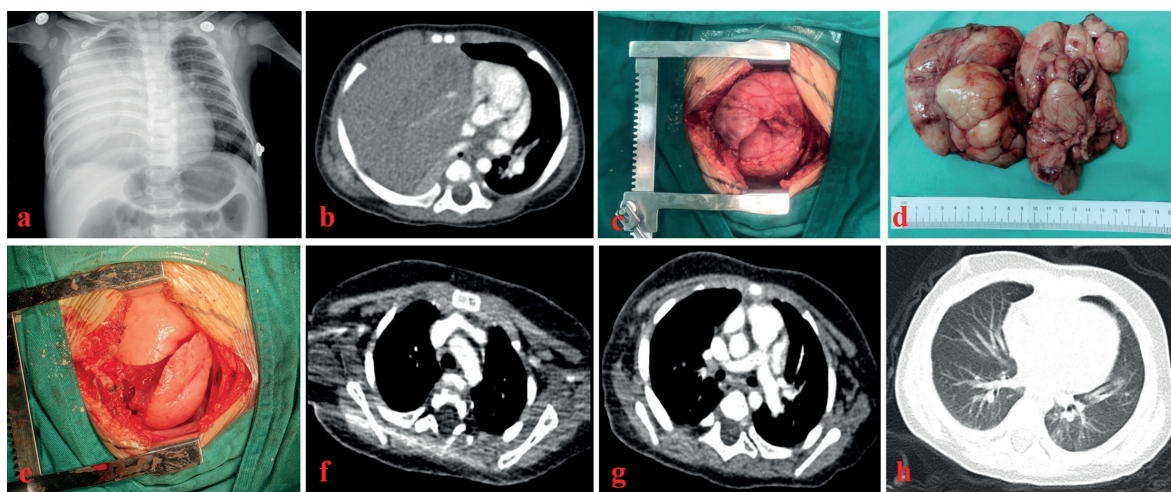
A 3-month-old male infant was admitted to our department on July 20th 2019, with a chief

complaint of gradually increasing polypnea over 9 days, especially after crying or aggravating activities. Without any specific past medical history or family history, the boy weighed 7 Kg on admission, with a height of 65 cm. Physical examinations revealed absent breath sounds in the right hemithorax. Laboratory investigations demonstrated a slight leukocyte rise of  $13.29 \times 10^9/L$  with 81.3% lymphocytes, while tumor markers such as alpha fetoprotein and neuron-specific enolase were in the normal range. Chest X-ray showed a large intrathoracic soft tissue shadow predominantly on the right side, occupying most of the right hemithorax (Fig. 1a).

A percutaneous fine-needle biopsy guided by color Doppler ultrasonography (US) was performed for this infant on July 24th 2019, in which 6 pieces of tissues from different directions inside the lesion were obtained to identify diagnosis. This patient was transferred

to a pediatric medical ward on July 26th 2019 and prepared to receive targeted antitumor chemotherapy based on biopsy results. Unexpectedly, proliferating lymphocytes and Hassall's corpuscles were seen microscopically in the biopsy tissues, which were immunohistochemically positive for CD3, CD19, CD20, CD99, TdT, PCK and Ki67 (>90%) (Fig. 2a-2h). The fluorescence in situ hybridization (FISH) of EBER 1/2 was also negative and gene rearrangement (PCR+GENESCAN) detected no TCRG amplification peak, which further supported the pathological diagnosis of TTH.

On August 27th 2019, this infant was referred to our department again for surgical resection by his family. Thoracic contrast-enhanced computed tomography (CT) was carried out, which showed a solid inhomogeneous predominantly hypodense hypervascularized soft tissue mass in the right thoracic cavity. This lesion was contiguous to the anterior



**Fig. 1.** a. Chest X-ray showed a large intrathoracic soft tissue shadow predominantly on the right side, involving most of the right hemithorax. b. Thoracic contrast-enhanced CT detected a solid predominantly hypodense, heterogeneous, hypervascularized soft tissue mass in the right thoracic cavity, significantly compressing the right lung with complete atelectasis and compressing the heart and large blood vessels with mediastinal shift towards the left. c. Exploratory thoracotomy found that a giant mass originating from the mediastinum filling most of the right thoracic cavity, pushing the right lung backwards and upwards. d. The mass was lobulated, fatty and soft in texture with clear boundary and complete capsule, measuring about  $17 \times 11 \times 4$  cm and 240g in weight. e. After resection of the whole mass, the right lung immediately re-expanded well with normal function. f. Four months after second operation, thoracic contrast-enhanced CT detected no recurrence and residual of lesion in the mediastinum or thoracic cavity. g. Ten months after second operation, thoracic contrast-enhanced CT also detected no recurrence and residual of lesion in the mediastinum or thoracic cavity. h. The patient's right lung expanded well 4 months after his second operation.

mediastinum, significantly compressing the right lung with complete atelectasis and squeezing the heart and large blood vessels with mediastinal shift towards the left, while the normal thymus was not well identified (Fig. 1b).

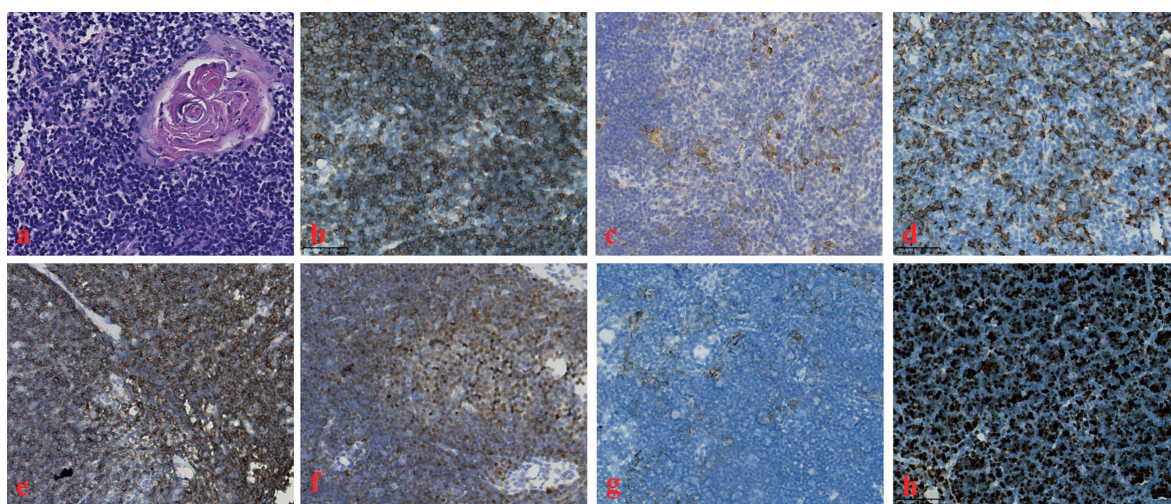
On August 30th 2019, under general inhalation anesthesia with endotracheal intubation, we performed a right anterolateral exploratory thoracotomy for this infant, in which a giant mass originating from the mediastinum was detected (Fig. 1c). The mass occupied most of the right thoracic cavity, leading to the right lung being visibly pushed backwards and upwards. Unfolding the mediastinal pleura, the mass was lobulated, fatty and soft in texture with clear boundary and complete capsule, which was compatible with that of thymus. During the operation, the fast-frozen pathologic examination from tissues of the mass indicated thymus hyperplasia once again. Finally, thymectomy with removal of homogeneous pale tissue was performed successfully for the infant, in which the whole mass measured about  $17 \times 11 \times 4$  cm in volume and 240g in weight (Fig. 1d). After resection, his right lung immediately re-expanded with normal function (Fig. 1e).

The postoperative course of this infant was uneventful. This patient was transferred to a general ward from the intensive care unit on the fifth postoperative day with a normal respiratory pattern and discharged from our hospital on September 8th 2019. The postoperative pathological report from the surgical specimen by both morphological study and immunohistochemical staining confirmed the diagnosis of TTH as well, which was in agreement with the previous results by fine-needle biopsy (Fig. 2). Ten months after the second operation, the boy had no new symptom and recurrence was detected. The chest CT detected no recurrence and residual of lesion in the mediastinum or thoracic cavity (Fig. 1f; Fig. 1g), and his right lung expanded well (Fig. 1h).

Patient has provided informed consent for publication of the case.

## Discussion

Located in the anterior mediastinum, the thymus embryologically derives from the ventral pouch of the third and fourth branchial arch. The size and weight of thymus varies with age. For a newborn, the mean weight of thymus is approximately 15 g. For infant at 1 to 3 years,



**Fig. 2.** Pathological analysis and immunohistochemical staining of the lesions by 400-fold optical microscope: **a.** Hematoxylin and eosin stain; **b.** Strong expression of CD3; **c.** Strong expression of CD19; **d.** Strong expression of CD20; **e.** Strong expression of CD99; **f.** Strong expression of TDT; **g.** Strong expression of PCK; **h.** Strong expression of Ki-67 (>90%).

normal thymus weight ranges between 23 and 55 g  $\pm$  13 g. Thymus gradually involutes during the first 3 to 4 years of life.<sup>1,2</sup> The thymus of a 3-month-old boy in our study weighed 240 g, notably beyond the average.

Thymus is the primary site of T-cell proliferation and maturation, whose hyperplasia has been usually defined by three classifications.<sup>3,5,7</sup> One is TTH with distinct increase in both size and weight, which retains normal microscopic and immunohistochemical appearances. The second one is lymphoid hyperplasia consisting of lymphoid cells with germinal centers predominates, regardless of the size or weight of thymus. The third one is lymphoepithelial sialadenitis like thymic hyperplasia. The second classification is often associated with myasthenia gravis, while the present case fell into the first category. As in our case (Fig. 2a-2h), TTH is histologically normal thymic tissue, which is composed of lobules with clearly demarcated cortex, medulla, and Hassall corpuscles.<sup>5</sup> Referring to the radiologic findings, TTH usually demonstrated a massively enlarged lesion extending from anterior mediastinum to the right upper and middle pleural cavity with underlying lung collapse without compression of the airway.<sup>8</sup> The present case showed similar imaging results, which was also rather difficult to be distinguished with other thymus masses preoperatively (Fig. 1a, 1b).

As a variant of TTH, MTTH is usually asymptomatic but occasionally produces symptoms related to compression of adjacent structures, such as dyspnea, dysphagia, pulmonary infections, or less commonly as an incidental finding.<sup>6</sup> Although there are no generally accepted definitions of MTTH, the following guidelines have been proposed in the literatures:<sup>5-8</sup> (i) the thymus should be greater than the heart shadow on posterior-anterior chest radiograph; (ii) it should weigh several times the expected weight for the age of the patient; (iii) it should represent more than 2% of the body mass. According to the description of clinical features above, our case met all three criteria.

The clinical manifestations and instrumental examinations of MTTH are atypical, which is often misdiagnosed as either anterior mediastinal tumor-like lesions, such as thymic lymphoma, thymoma, and germ cell tumors, or other causes of thymus enlargement, such as myasthenia gravis.<sup>2,8</sup> Distinguishing these entities requires pathological analysis of issues by fine-needle biopsy or surgical resection. In the present study, mediastinal malignancy was highly suspected for this infant at the beginning, while analysis by percutaneous US-guided fine-needle biopsy was compatible with TTH. This situation might be caused by the misdiagnosis from insufficient or inaccurate biopsy tissues, which was however confirmed once again by the analysis of resected specimens from his second operation. Finally, this boy was managed surgically with complete excision of thymus, as advocated by most authors.<sup>5,8-10</sup>

It has been reported that the age of cases with MTTH is predominantly between 1 and 15 years, while those before 1 year or after 15 years rarely occurs.<sup>1,2,8</sup> To the best of our knowledge, there were only 10 cases with MTTH reported in the literature between 1975 and 2020 in children aged <1 year of life, including our present case (Table I).<sup>2,5,6,11-16</sup> We identified 7 males and 3 females, whose mean age at diagnosis was 5.9 months, ranging from the youngest one of 1 month to the eldest of 11 months. Nine out of 10 presented initial symptoms or signs related to the respiratory system and 6 patients showed respiratory distress. Only 3 patients received glucocorticoids therapy which all failed to shrink the volume of thymus and to relieve the symptoms. Finally, all patients were successfully treated by surgical thymectomy without any postoperative complications. The mean weight and mean largest diameter of resected thymus was 296.4 g (ranging from 200 g to 550 g) and 14 cm (ranging from 8.5 cm to 18 cm), respectively. According to the available prognostic data of each case, 8 patients were thoroughly asymptomatic at follow-up (80%). One patient with Beckwith-Wiedemann Syndrome had a hepatic hemangioma and was

**Table I.** Clinical features of MTHH in children aged <1 year of life, including present case.

Authors	Date	Sex	Age	Symptoms	Treatments	Thymus size	Prognosis (age)
Katz et al <sup>11</sup>	1977	M	7 mo	Hepatomegaly	Surgical thymectomy	224 g 9 × 8 × 6 cm	Asymptomatic (4 y)
Lamesch et al <sup>12</sup>	1982	F	7 mo	Respiratory distress	1. Steroid (ineffective) 2. Surgical thymectomy	230 g 18 × 11 × 8.5 cm	Asymptomatic (7 y)
Linegar et al <sup>6</sup>	1993	F	2 mo	Respiratory distress	Surgical thymectomy	220 g	Asymptomatic (3 mo)
Lee et al <sup>13</sup>	1996	M	11 mo	Fever and upper respiratory symptoms	Surgical thymectomy	500 g	Asymptomatic <sup>A</sup>
Woywodt et al <sup>14</sup>	1999	M	11 mo	Pneumonia	Surgical thymectomy	550 g 17 × 5 × 3 cm	Asymptomatic (6 y)
Regal et al <sup>2</sup>	2007	M	5 mo	Respiratory distress	Surgical thymectomy	380 g	Asymptomatic (2 y)
Tan et al <sup>5</sup>	2010	F	9 mo	Fever and upper respiratory symptoms	1. Steroid (ineffective) 2. Surgical thymectomy	200 g 17.5 × 11 × 5 cm	Asymptomatic (at the discharge from hospital)
Sayed et al <sup>15</sup>	2016	M	3 mo	Respiratory distress, failure to thrive	Surgical thymectomy	219.7 g 14 × 12 × 5 cm	Hepatic hemangioma and managed conservatively <sup>B</sup>
Weis et al <sup>16</sup>	2017	M	1 mo	Respiratory distress	1. Steroid (ineffective) 2. Surgical thymectomy	200 g 8.5 × 7.5 × 3.8 cm	Recurrence and 2nd resection, asymptomatic (1 y) <sup>C</sup>
Present case	2020	M	3 mo	Respiratory distress	Surgical thymectomy	240 g 17 × 11 × 4 cm	Asymptomatic (1 y)

<sup>A</sup>: Author did not list time of follow-up.

<sup>B</sup>: Patient was clinically diagnosed as MTHH with Beckwith-Wiedemann syndrome. At follow-up, he presented with hepatic hemangioma which was managed conservatively.

<sup>C</sup>: Patient showed recurrence of MTHH soon after first surgery. A second surgical resection was performed again. Child asymptomatic at 1y follow-up.

MTHH: massive true thymic hyperplasia, M: male, F: female.

managed conservatively. One patient showed a recurrence of MTHH soon after the first surgery and a second surgical resection was performed successfully, who was asymptomatic at 1 year old.

In conclusion, we described a case of 3-month-old infant who was clinically diagnosed with MTHH. Together with our present one, there were only 10 cases with MTHH reported in the literature between 1975 and 2020 in children aged

<1 year of life. Patients gender in MTHH had an obviously male predominance. Glucocorticoids might be ineffective, while surgical thymectomy could be perfectly performed for the patients. The prognosis of MTHH was very well.

#### Author contribution

In this paper, M. Yang and L. Zeng. Contributed equally to this work as co-first authors: ZCXu; contributed as senior author. MY, LZ; extracted

the data and wrote the manuscript together: BX; made the figures: YJi; made the references review: BX, ZCXu; had important intelligent contributions and critically revised the manuscript. All authors in read and approved the final manuscript.

### Conflicts of interest

The authors declared no conflict of interest.

### REFERENCES

1. Riazmontazer N, Bedayat G. Aspiration cytology of an enlarged thymus presenting as a mediastinal mass. *Acta Cytol* 1993; 37: 427-430.
2. Regal MA. Gigantic enlargement of the thymus gland. *Saudi Med J* 2007; 28: 1587-1589.
3. Judd RL. Massive thymic hyperplasia with myoid cell differentiation. *Human Pathol* 1987; 18: 1180-1183.
4. Pedroza Meléndez A, Larenas-Linnemann D. Thymus hyperplasia, differential diagnosis in the wheezing infant. *Allergol Immunopathol (Madr)* 1997; 25: 59-62.
5. Tan Z, Ying LY, Zhang ZW, Li JH, Gao Z, Qi JC. True thymic hyperplasia in an infant. *J Pediatr Surg* 2010; 45: 1711-1713.
6. Linegar AG, Odell JA, Fennell WM, et al. Massive thymic hyperplasia. *Ann Thorac Surg* 1993; 55: 1197-1201.
7. Weissferdt A, Moran CA. Thymic hyperplasia with lymphoepithelial sialadenitis (LESA)-like features: a clinicopathologic and immunohistochemical study of 4 cases. *Am J Clin Pathol* 2012; 138: 816-822.
8. Tadiotto E, Clemente M, Pecoraro L, Piacentini G, Degani D, Pietrobelli A. Massive thymic hyperplasia in a 15-month-old boy: case report and literature review. *Clin Case Rep* 2019; 7: 27-31.
9. Lee Y, Moallem S, Clauss RH. Massive hyperplastic thymus in a 22-month-old infant. *Ann Thorac Surg* 1979; 27: 356-358.
10. Szarf G, Mussi de Andrade TC, De Oliveira R, Ota LH, Lederman HM. Massive thymic hyperplasia presenting with respiratory insufficiency in a 2-year-old child. *Thorax* 2010; 65: 555-556.
11. Katz SM, Chatten J, Bishop HC, Rosenblum H. Report of a case of gross thymic hyperplasia in a child. *Am J Clin Pathol* 1977; 68: 786-790.
12. Lamesch AJ. Massive thymic hyperplasia in infants. *Z Kinderchir* 1983; 38: 16-18.
13. Lee YM, Koh MT, Omar A, Majid A. Hyperplasia of thymic gland. *Singapore Med J* 1996; 37: 288-290.
14. Woywodt A, Verhaart S, Kiss A. Massive true thymic hyperplasia. *Eur J Pediatr Surg* 1999; 9: 331-333.
15. Sayed S, Sharma V, McBride CA, Levitt D, Alphonso N. Massive thymic hyperplasia in a neonate with Beckwith-Wiedemann syndrome. *J Paediatr Child Health* 2016; 52: 90-92.
16. Weis CA, Märkl B, Schuster T, Vollert K, Ströbel P, Marx A. "Echte Thymushyperplasie" Differenzialdiagnose der thymusvergrößerung bei Säuglingen und Kindern. *Pathologe* 2017; 38: 286-293.