Case Report

Asymptomatic lipofibroadenoma in a 17-year-old male: a case report and literature review of a rare entity

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Background: The most common thymic tumours, thymomas, are derived from thymic epithelium and are generally low-grade neoplasm. Frankly malignant tumours, thymic carcinomas are rarer still. Exceedingly rare thymic tumours contain a mesenchymal tissue component such as fibrous connective tissue and/or mature fat. Lipofibroadenoma (LFA) is a very rare mixed epithelial-mesenchymal thymic tumour, included in the category of thymic epithelial tumors. LFA in addition to a mature adipocytic component, contains variable epithelial and mesenchymal tissue components. Owing to the presence of an epithelial component in LFA, this entity, in contrast to thymolipoma, is included in the World Health Organization (WHO) category of thymic epithelial neoplasm. Currently only 12 LFA cases have been described. The 12 previously reported cases all behaved in a benign fashion, although four cases were associated with a conventional type of thymoma. We here present a new, 13th, case of LFA.

Case Description: The LFA was discovered incidentally in a previously healthy 17-year-old male after investigations for suspected pneumonia. On imaging a mass was discovered in the anterior mediastinum which was subsequently surgically removed. The resected tumour was extensively investigated, including the first instance of full molecular analysis of this rare entity and all available literature on LFA was sourced to provide a comprehensive overview. The histology of this LFA was similar to previously described cases. No gene mutations or rearrangements were identified. The patient made an uneventful recovery and after 13 months of follow-up remained well.

Conclusions: An additional, 13th case of LFA is presented. Based on the available literature it appears that LFA may be considered a benign composite thymic tumour, although the combination of an additional conventional thymoma component may warrant closer follow-up.

Keywords: Mediastinum; thymus; thymoma; case report

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Introduction

The vast majority of thymic tumours fall within the category of thymoma. These are primary epithelial neoplasms often admixed with an immature lymphocytic component, thus reflecting to a certain degree organoid thymic differentiation. The World Health Organization (WHO) recognizes two thymic tumours with an adipose component, thymolipoma is considered a primary adipocytic tumour, while lipofibroadenoma (LFA) is included in the category of thymic epithelial tumours but which contains an adipocytic component (1). We here present an incidentally discovered mediastinal tumour in a young male which was resected and subsequently diagnosed as an LFA. This is to the best of our knowledge the thirteenth case of LFA reported in the literature since this entity was first described in 2001 (2) (*Table 1*), and the first case to be analyzed by next-generation sequencing and RNA sequencing (RNAseq). We present the following case in accordance with the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-22-32/rc).

Case presentation

A 17-year-old previously healthy Caucasian male underwent imaging for suspected pneumonia. The magnetic resonance imaging (MRI)-scan (*Figure 1A*) and computed tomography (CT)-scan (*Figure 1B*) showed a hypointense (MRI)/hypodense (CT) tumour with focally more intense (MRI)/denser (CT) areas in the anterior mediastinum, abutting the aortic arch, pulmonary trunk and left ventricle. There was no mediastinal lymphadenopathy and there were no signs of pleural effusion. Based on the imaging investigations, the differential diagnosis included lipomatosis, lipoma/thymolipoma and liposarcoma. As serology did not reveal elevated tumour markers, a germ-cell tumour was considered unlikely. Based on the clinical and radiological findings primary thoracoscopic resection of the tumour and adjacent thymic tissue was performed through the left pleural cavity. After dissection and sealing of the feeding vessel using monopolar diathermy and a bipolar sealing device (Ligsure®, Medtronic, Minneapolis, MN, USA), the specimen was retrieved through an enlarged trocar opening using a thoracoscopic specimen retrieval bag. The recovery was uneventful. The patient was discharged on the third postoperative day.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A thinly encapsulated soft tumour of 12.5×8.0×2.5 cm weighing 153 g was received (*Figure 2A*), which on sectioning mainly consisted of pale yellow fatty tissue with areas of pink-grey fibrous tissue (*Figure 2B*). Fresh tissue, checked by frozen section for the presence of representative constituents, was procured for molecular studies, the specimen was subsequently routinely fixed and processed for histology. A tumour with multiple components was seen in microscopy (*Figure 3A-3D*), areas of mature fat were admixed with pauci-cellular connective tissue with scattered collections of small lymphocytes. The proportion of fatty tissue to collagenous connective tissue varied considerably within the tumour (*Figure 3A*). Throughout these components branching interconnected cords of small epithelial cells were present (*Figure 3B*), occasionally associated with small solid collections of non-atypical spindled cells (*Figure 3C*). Scattered Hassall's corpuscles were present (*Figure 3D*), typically located within lymphoid aggregates. Scattered small calcifications were noted. There was no necrosis, no atypia or nuclear hyperchromasia. Mitotic activity was extremely low. The strands and small foci of spindled cells stained for cytokeratin (pan-cytokeratin AE1-AE3) and p63 (*Figure 4A*,*4B*). The lymphoid aggregates were mainly composed of immature T-cells (CD3/TdT positive) often with small collections of CD20 positive B-cells (*Figure 4C*,*4D*). Molecular analysis was performed by whole exome sequencing (WES) and RNAseq on non-selective tumour tissue samples. For WES total DNA was isolated using the AllPrep DNA/RNA/Protein Mini Kit (Qiagen) according to standard protocol on the QiaCube (Qiagen). DNA-seq libraries were generated with 150 ng DNA using the KAPA HyperPrep Kit in combination with the HyperExome capture kit (Roche) and subsequently sequenced on an NovaSeq 6000 system (2×150 bp) (Illumina). The DNA sequencing data of the tumor and the normal (DNA extracted from blood) were processed as per the GATK 4.0 best practices workflow for variant calling, using a wdl and cromwell based workflow (https://gatk.broadinstitute.org/hc/en-us/sections/360007226651-Best-Practices-Workflows). This included performing quality control with Fastqc (version 0.11.5) to calculate the number of sequencing reads and

Table 1 Published cases of LFA

No.	Authors	Year	Gender, age (years)	Symptoms, duration	Size	Associations	Follow-up [months]
1	Kuo and Shih (2)	2001	Male, 62	Dyspnea, dizziness, PRCA	ND	B1 thymoma, PRCA	No recurrence of tumor [80], PRCA relapse 2× after removal of tumor
2	Onuki *et al*. (3)	2009	Male, 32	Incidental finding in work-up for pneumonia, 6 months	3 cm	–	ND
3	Wang *et al*. (4)	2009	Male, 56	Cough, expectoration, 2 weeks	4.5 cm	B1 thymoma	NED [24]*
4	Aydin *et al*. (5)	2012	Female, 23	Chest pain, dyspnea, 6 months	21 cm, 2,180 g	B1 thymoma (proposed composite B1 thymoma and lipofibroadeoma)	NED [12]
5	Qu *et al*. (6)	2013	Male, 21	Asymptomatic, incidental finding	10 cm	–	NED [46]
6	Makdisi *et al*. (7)	2015	Male, 20	Acute onset of fever and cough	23 cm, 670 g	–	NED [6]
7	Hui *et al*. (8)	2018	Male, 29	Cough, expectoration 6 months	6.5 cm	B1 thymoma	ND
8	Hamada *et al*. (9), Kurebayashi *et al*. (10)	2018, 2021	Female, 55	Asymptomatic, incidental finding on PET-CT	4.5 cm	Thymic hyperplasia	NED [12]
9	Kojima *et al*. (11)	2018	Male, 29	Asymptomatic	6 cm	–	ND
10	Hakiri *et al*. (12)	2021	Male, 28	Asymptomatic, incidental finding	9 cm	–	NED [6]
11	Matyjek *et al*. (13)	2021	Female, 35	Fatigue, cough	26 cm	ANCA-associated vasculitis with renal involvement	NED [12]; progressive renal deterioration
12	Bolca *et al*. (14)	2021	Female, 64	Progressive dyspnea	16 cm, 2,800 g	–	NED [48]
13	Current report	2022	Male, 17	Incidental finding in work-up for pneumonia	12.5 cm, 153 g	–	NED [13]

*, follow-up estimated from publication date. LFA, lipofibroadenoma; PRCA, pure red cell aplasia; ND, no data; NED, no evidence of disease; PET, positron emission tomography; CT, computed tomography; ANCA, anti neutrophil cytoplasmic antibody.

the insert size Picard (version 2.20.1) for DNA metrics output and MarkDuplicates (15). mRNA sequencing was performed as previously described (16). In brief, total RNA was isolated using the AllPrep DNA/RNA/Protein Mini Kit (Qiagen) according to standard protocol on the QiaCube (Qiagen). RNA-seq libraries were generated with 300 ng RNA using the KAPA RNA HyperPrep Kit with RiboErase (Roche) and subsequently sequenced on an NovaSeq 6000 system (2×150 bp) (Illumina). The RNA-seq data were processed as per the GATK 4.0 best practices workflow for variant calling, using a wdl and cromwell based workflow (https://gatk.broadinstitute.org/hc/en-us/sections/360007226651-Best-Practices-Workflows). This included performing quality control with Fastqc (version 0.11.5) to calculate the number of sequencing reads and the insert size Picard (version 2.20.1) for RNA metrics output and MarkDuplicates (15). The raw sequencing reads were aligned using STAR (version 2.7.0f) to GRCh38 and gencode version 29 (16). Finally, expression counts were determined at gene level using Subread Counts (17). Fusion

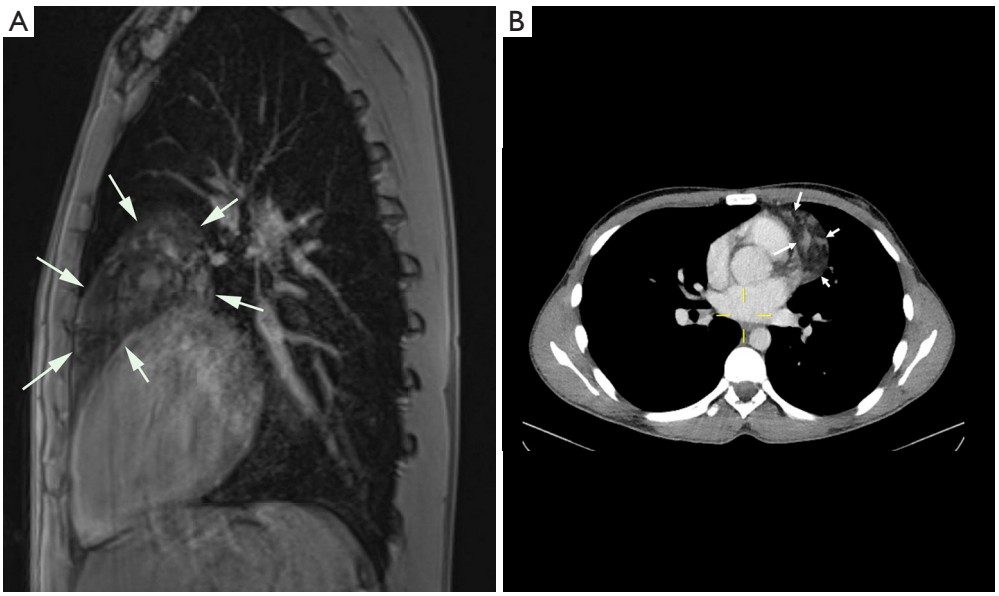

Figure 1 MRI and CT-scan. (A) Post-contrast T1 vibe (volumetric interpolated breath-hold examination) fat saturated sagittal MR-image, depicting a supra-cardial fatty mass (indicated by arrows). (B) Contrast-enhanced transverse CT-image showing the left para-cardial located low density mass (indicated by arrows). MRI, magnetic resonance imaging; CT, computed tomography; MR, magnetic resonance.

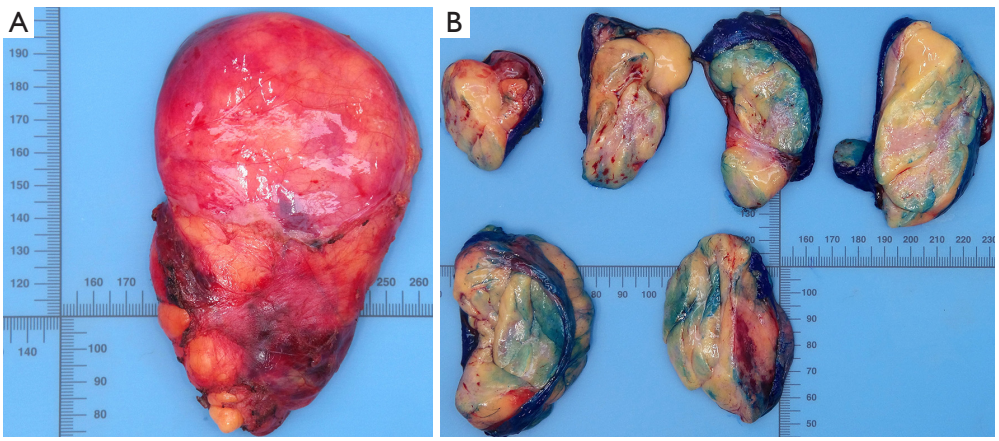

Figure 2 Gross image of resected tumour. (A) Thinly encapsulated 12.5 cm excised tumour. (B) On sectioning a predominantly fatty specimen is seen with focally grey fibrous areas.

gene detection was performed using STARfusion.

No relevant somatic mutations or copy number variation (CNV) were detected through WES, no gene rearrangements were identified by RNAseq. Based on the findings a diagnosis of thymic LFA was made. Following surgery the patient made a good recovery and at 9 months follow-up there was no evidence of disease.

Discussion

The vast majority of thymic neoplasms are derived from thymic epithelium. Of these most are thymomas and behave as low-grade neoplasms, of which different histological subtypes are recognized in the WHO classification (1). A lymphocytic component is present in most subtypes of

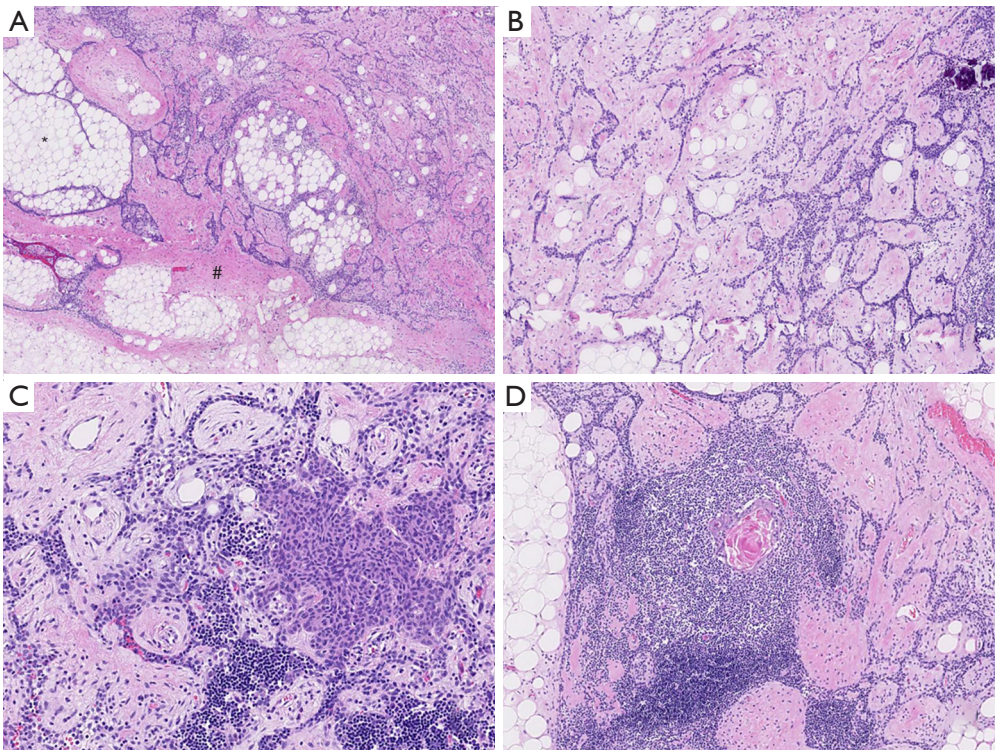

Figure 3 Histology. (A) Fibro-fatty tissue with ramifying cords of epithelial cells. Mature fatty tissue, present in several areas in this slide (a single area indicated by *). Pink fibrous collagenous tissue is indicated (#). Darker branching strands of epithelial cells ramify through both fibrous and fatty tissue. (B) Scattered small calcifications were present, again note the slender strands of epithelial cells. (C) Discrete collections of spindled epithelial cells, comparable to those of a spindle cell thymoma. (D) Lymphoid component with a Hassall's corpuscle. HE stained sections (A,B: low power view; C,D: medium power view). HE, hematoxylin-eosin.

thymoma reflecting differentiation along the lines of the normal thymus. However, mesenchymal tissue does form part of the thymoma spectrum and as such is exceedingly rare in a primary thymic tumour, the only exception being somatic mesenchymal tissue elements in thymic germ-cell tumours. Only two primary non germ-cell thymic tumours with a mesenchymal component have been conclusively described, thymolipoma and LFA. It has been suggested that a third malignant mesenchymal (adipocytic) tumour in the mediastinum may originate in the thymus (thymoliposarcoma) (18).

Thymolipoma is a primary thymic adipocytic neoplasm consisting of mature fat which may reach a large size before producing symptoms. While scattered islands of otherwise normal thymic tissue are commonly present within the fatty tissue of thymolipoma, these are not thought to be part of the neoplasm but rather entrapped normal thymic tissue. Recently a case was described with an extensive, partly organoid, thymic epithelial component combined with areas in keeping with thymolipoma, thus blurring the border between thymoma and thymolipoma (19). Support for the neoplastic nature of thymolipoma is the identification of a *HMGA-2* mutation (20). Variants of thymolipoma have been described with an excess of connective tissue, thymofibrolipoma, and with a conspicuous vascular component, thymohemangiolipoma (21-24).

In contrast to thymolipoma, LFA contains a characteristic epithelial component in addition to the lipomatous component. Therefore, in the current WHO classification thymolipoma is considered a thymic mesenchymal tumour while LFA is classified as a thymic epithelial tumour (1).

In all documented cases the epithelial component of LFA consists of small bland cells with sparse cytoplasm arranged in interconnected strands and cords ramifying through the connective tissue and fat. The typical branching epithelial strands, somewhat reminiscent of mammary fibroadenoma, prompted the designation LFA in 2001 (2). The epithelial strands are intimately associated with both

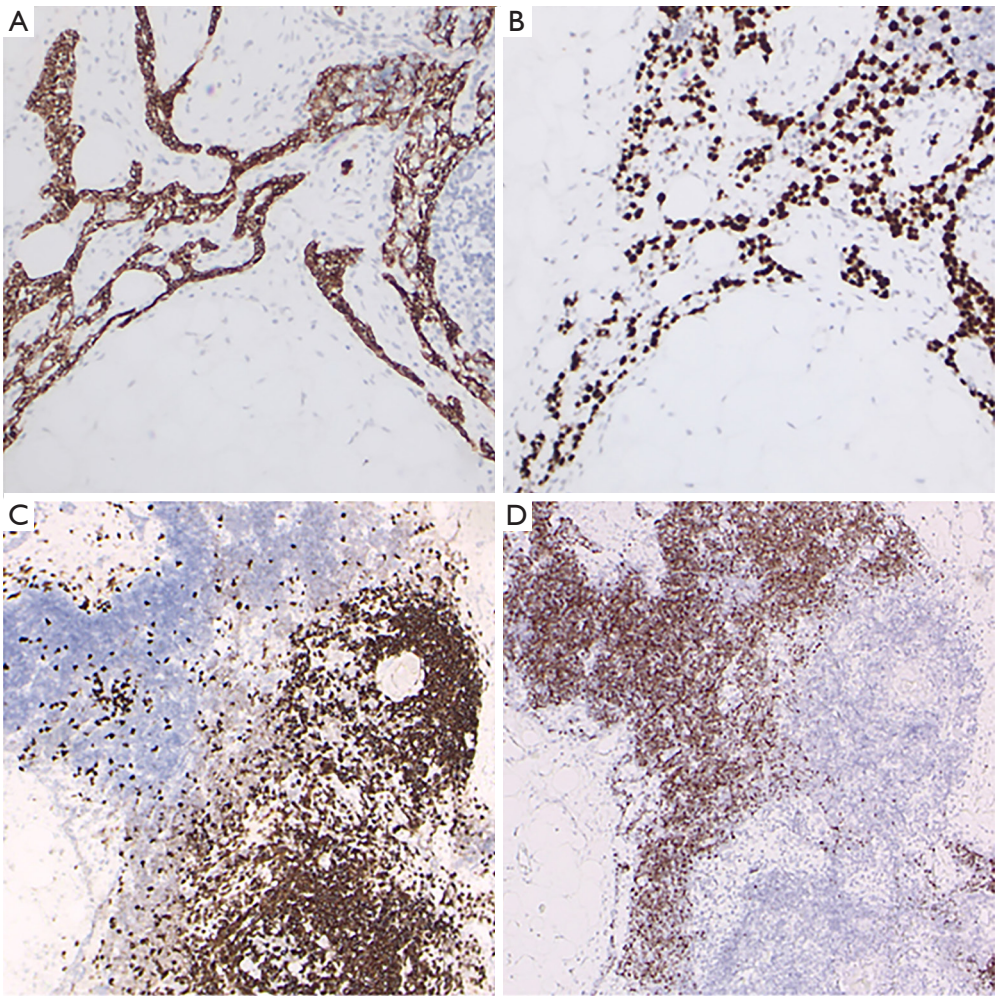

Figure 4 Immunohistochemistry. The epithelial strands are highlighted in the AE1/AE3 cytokeratin (A) and p63 (B) stains (medium power views). The lymphoid component shows a mixed B-cell (CD20 positive) population (C) combined with an immature (TdT positive) T-cell population (D) (medium power views).

the lipomatous tissue and pauci-cellular connective tissue. Features suggesting malignancy such as atypia, conspicuous proliferative activity and necrosis have not been described in LFA. The lipomatous component consists of mature fat cells devoid of lipoblasts. Pronounced calcifications were described in a single report, prompting the consideration of a germ-cell tumour (12). Small calcifications were previous described in LFA (11), and were also present in our case. In the case we present here small foci with increased cellularity were present, composed of more spindled cells, reminiscent of those seen in type A/AB thymoma. The lymphocytic component in LFA is generally poorly developed, immature TdT positive lymphocytes may be present (10-12), as in the case presented here, or may be absent (4,7-9).

Whether thymofibrolipoma and LFA are separate tumour entities or form a spectrum of composite lipomatous thymic tumours is not clear. Makdisi *et al.* group thymofibrolipoma together with LFA (7). Indeed, the images in the article by Moran, Zeren & Koss show histological overlap with LFA with strands of cells in fibrous tissue, suggestive of a thymofibrolipoma-LFA tumour continuum (22). However, this feature is not clearly seen in the thymofibrolipoma case presented by Kang *et al.* (21).

Patients with LFA are usually young (range, 17–64 years, median age 29 years), with a male predominance (4/9 female/male ratio) (2-12,14). Most LFA cases described to date were discovered incidentally by investigations performed for unrelated symptoms. If symptoms were

present, these were non-specific consisting of cough or dyspnea. A single case of red cell aplasia has been reported, but in this case the LFA was associated with a B1 thymoma, which may well account for the para-neoplastic pure red cell aplasia (2).

Interestingly, in four of the hitherto described cases, the LFA was associated with a B1 thymoma, which given the rarity of both thymoma and LFA is suggestive of a pathogenetic relationship (details of reported cases in *Table 1*) (2,4,5,8). The follow-up of all reported cases after surgical removal of the LFA is favorable, no recurrences have been reported and patients made a good recovery. While the patient described in the report by Matyjek and co-workers made an initial good recovery from the operative procedure to remove a large LFA, she did suffer progressive anti neutrophil cytoplasmic antibody (ANCA)-vasculitis associated renal failure (13). Although it was suggested that the vasculitis may have been associated with the LFA given the co-occurrence of two rare diseases, this may be contested as the ANCA-associated vasculitis progressed after removal of the LFA. Current evidence suggests that LFA behaves in a benign fashion and only limited follow-up after removal is indicated. In those cases where as associated sub-type is present, as in the three reported cases associated with B1 thymoma it would be prudent to base the follow-up on the associated thymoma.

The nature of LFA is uncertain. The mixed composition of LFA could be taken as indicative for a hamartomatous origin rather than a true neoplasm. However, the circumscription, encapsulation and occasional large size are more in keeping with a neoplastic process. In the case presented here we did not identify genetic aberrations, specifically no *HMGA-2* mutation was found, as described recently in thymolipoma, nor were CNVs documented. In a single recently described LFA case no fusion transcripts were detected (13), taken together with our case, there are currently no features which support a neoplastic process.

Conclusions

In conclusion, we report the 13th case of a rare mixed epithelial-mesenchymal tumour, LFA. The reported case bears many similarities to reported cases and adds to the awareness of this rare entity.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-22-32/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-22-32/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-22-32/coif). MAdB serves as an unpaid editorial board member of *Mediastinum* from March 2022 to February 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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