Diagnostic Pathology

CASE REPORT

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Rare atypical type a thymoma: a case report and literature review

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Abstract

Background An atypical type A thymoma variant was recently added to the World Health Organization classification of type A thymoma in 2015. This novel form of type A thymoma presents with hypercellularity, increased mitotic activity, and necrosis. In particular, necrosis seems to be related to postoperative recurrence and metastasis, but the clinical significance of these changes still needs to be studied.

Case presentation A 76-year-old man underwent thoracoscopic surgery for tumour resection due to an anterior mediastinal mass. Pathological examination revealed that the tumour invaded the surrounding thymic tissue. Cells were arranged in nest-like and whirl-like patterns, accompanied by prominent comedo-like necrosis, increased cell density, mild atypia, and a mitotic count of 4–6 per 10 high-power fields. Immunohistochemistry revealed positive expression of cytokeratin 19 and P63 in the tumour cells. Lymphocytes in the background were positive for CD3 and CD5, did not express terminal deoxynucleotide transferase, CD20, or CD117, and had an MIB-1 labelling index(LI) value of 15%. On the basis of these findings, the tumour was finally diagnosed as an atypical type A thymoma variant.

Conclusions We report a case of atypical type A thymoma and review the literature to enhance our understanding of and provide accumulated pathological data on this rare disease.

Keywords Thymoma, Type a thymoma, Necrosis, Atypia, Pathology

Background

Type A thymoma has been regarded as an indolent tumour with favourable prognosis. However, recent studies have revealed that some type A thymomas represent distant metastases or postoperative local recurrence [1, 2]. A pathological review of type A thymomas with postoperative tumour recurrence identified an aggressive subset of tumours; this atypical type A thymoma variant category was added to the World Health Organization (WHO) classification in 2015 [3]. At present, only 14 cases have been reported in the English literature, and no relevant studies have summarised the relevant characteristics of this tumour. We report a case of atypical type A thymoma and review the literature to enhance our understanding of and provide accumulated pathological data on this rare disease.

Case report

Case characteristics

A 76-year-old male was admitted to our hospital due to chest tightness and palpitations. Chest computed tomography (CT) revealed a nodule-like high-density shadow that measured 4.7 cm x 4.1 cm x 4 cm in the anterosuperior mediastinum (Fig. 1). The nodule exhibited uniform

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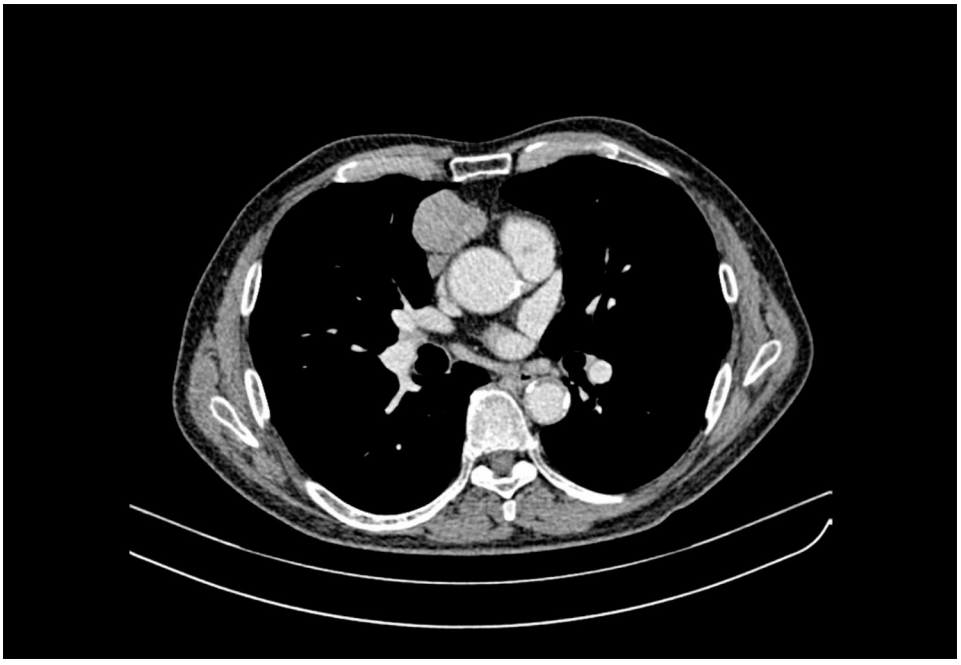

Fig. 1 CT image of the anterosuperior mediastinum showing the presence of a nodule-like high-density shadow with uniform density, a well-demarcated and smooth border, irregular morphology, and a clear peripheral fat gap

density, a well-demarcated and smooth border, and irregular morphology. A clear peripheral fat gap was also observed. Based on these findings, a diagnosis of thymoma was considered. Tumour resection was performed under thoracoscopy. Intraoperatively, the tumour capsule was found to be intact without invasion of the surrounding organs and was completely resected.

Pathological findings

Microscopic examination revealed that the capsule was partially fibrous and the tumor had invaded the surrounding thymic tissue (Fig. 2A). Cells were arranged in nest-like and whirl-like patterns (Fig. 2B) and accompanied by prominent comedo-like necrosis (Fig. 2C), calcification, increased cell density, and mild atypia. Nuclei were short spindle-shaped or oval-shaped and deeply stained and contained inconspicuous nucleoli. Perivascular spaces were not found, and the mitotic count was 4–6 per 10 high-power fields (HPFs). Immunohistochemistry revealed that the tumour cells had positive expression of cytokeratin 19 (CK19) and P63 (Fig. 3A). Lymphocytes in the background were positive for CD3 and CD5 (Fig. 3B), did not express terminal deoxynucleotide transferase (TdT), CD20, or CD117, and had an MIB-1 labelling index value of 15%. The patient was pathologically diagnosed with atypical type A thymoma. He was discharged 7 days postoperatively and was without recurrence at the 1-year follow-up.

Discussion and conclusions

Type A thymoma is a thymic epithelial neoplasm with variable growth patterns, composed of usually bland spindle/oval tumour cells with few or no admixed immature lymphocytes. Tumours are characterised by no (immature) lymphocyte-rich regions with dense, " impossibleto-count" TdT(+) lymphocytes; or at most 10% tumor regions with moderate immature lymphocyte counts [4]. Type A thymoma has been regarded as an indolent tumour with a favourable prognosis. However, there have been a few reports of postoperative recurrence and distant metastases [1, 2]. Recent global data have shown that approximately 1% of 443 patients with type A thymomas have stage IVB disease [5]. Cesar et al. reported spindle cell thymomas (WHO type A), just like any other histologic variant of thymoma, have a similar potential to become invasive tumors capable of spreading in or outside of the thoracic cavity [6]. To distinguish such unusual entities, atypical type A thymoma was newly classified as a subtype of thymomas in 2021. Atypical type A thymomas are defined as those with one or more of the following pathological features: (a) hypercellularity, (b) increased mitotic count, and (c) focal necrosis [7]. Type A thymoma is a relatively uncommon subtype, and atypical type A thymoma is even rarer, with only 14 English reports in the literature to date. Table 1 shows the results of the data analysis of the 15 reported cases (including the present case).

In clinical practice, atypical type A thymoma is often incidentally discovered during physical examination or

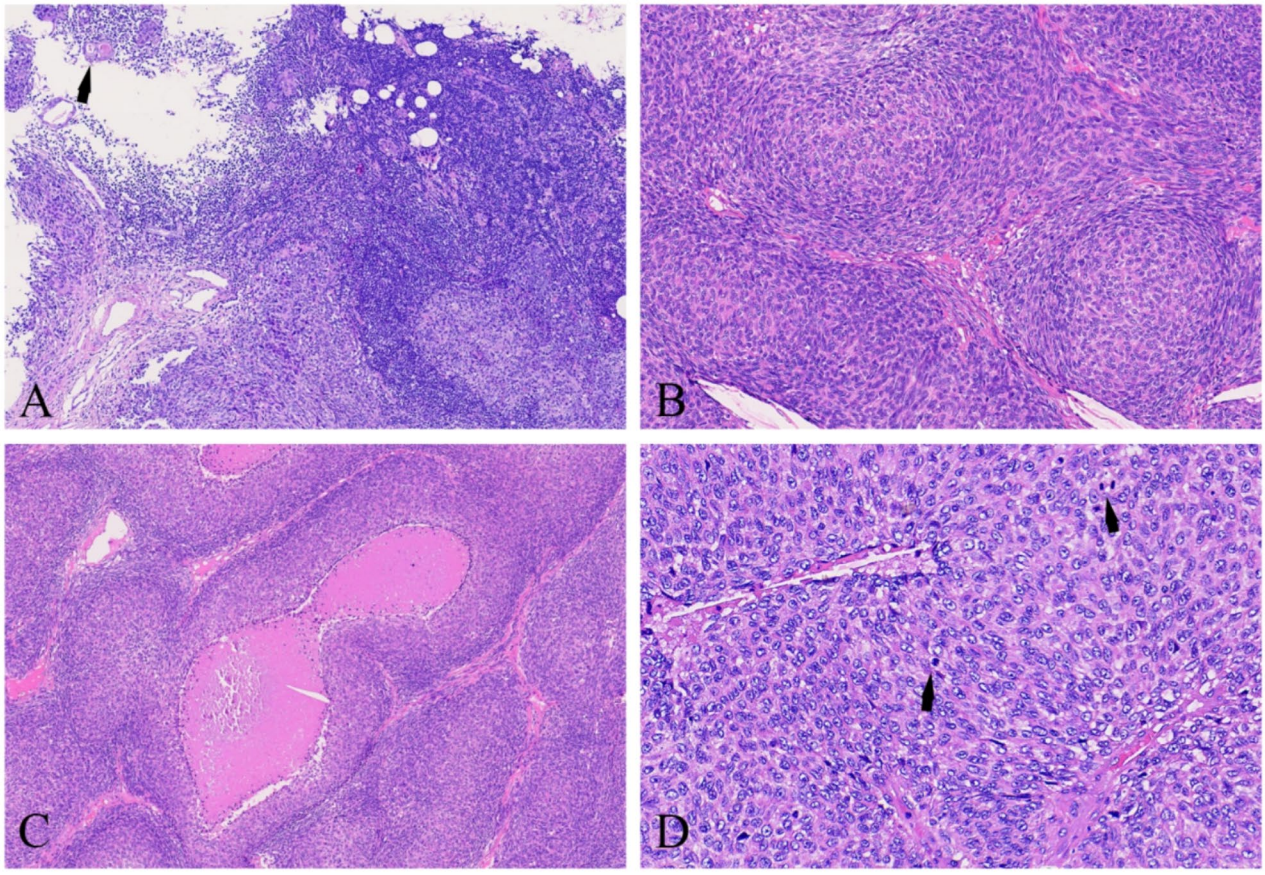

Fig. 2 Histological sections showing tumour invasion into the surrounding thymic issue. (**A**, 100×) The arrow indicates a thymic corpuscle. (**B**, 200×) Tumour cells exhibited increased density and a whirl-like arrangement. (**C**, 100×) Prominent comedo-like necrosis. (**D**, 400×) The arrows indicate mitosis

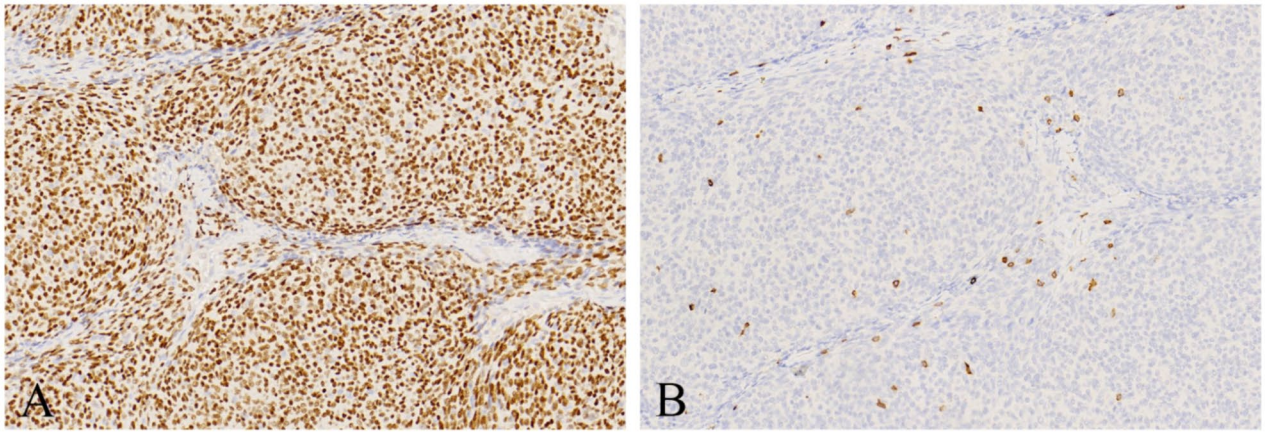

Fig. 3 Immunohistochemically stained sections showing (**A**, 200×) P63 expression in the tumour cells and (**B**, 200×) CD5 expression in background lymphocytes

during the investigation of other diseases. Only a minority of patients present with non-specific symptoms, such as cough or chest pain, and no patients have exhibited comorbid severe myasthenia gravis.The onset mainly occurred in middle or old age (35–84 years), with the average age at onset being 63 years. The reported cases consisted of slightly more men than women (9 vs. 6). Imaging diagnosis are primarily made through imaging modalities like CT and magnetic resonance imaging. However, these methods are inadequate for confirming

Table 1 Clinical manifestations and prognosis of 15 cases of atypical thymoma

Case No	Sample size	Gender	Age	Size (cm)	Necrosis	Mitotic activity (/10 HPFs)	Masaoka Stage	Follow-up (years)	Status	Metastasis
Makoto 2023 [25]	1	F	61	NA	N	5–6	II	15	A	Lung
Yanagiya 2021 [14]	1	M	53	2.6	N	9	IVB	1	A	Lung
Jimbo 2021 [18]	1	M	58	2.7	Y	6	IIA	2	A	N
Yanagiya 2020 [17]	1	M	68	8.5	NA	NA	III	3.5	A	Pericardial Sacrum bone
Chiappetta 2019 [19]	1	M	60	12.3	Y	NA	IVB	2	A	Vertebral
Shen 2018 [15]	2	F/M	NA/NA	7.5/10	NA/NA	5/4	I/I	1.75/1.4	A/A	N/N
Kawakita 2018 [20]	1	M	84	4.4	NA	14	IVB	1	A	Lung
Grajkowska 2017 [13]	1	F	66	13	Y	12	IIA	15	D	Lung Brain
Bürger 2017 [21]	2	M/F	66/67	7/NA	N/Y	4/N	IVB/IVB	3.75/NA	A/NA	Lung/Lung
Hashimoto 2017 [22]	1	F	35	6	Y	NA	I	6	A	Lung
Toyoda 2017 [24]	1	M	54	5.2	Y	7	IVA	1.5	A	Lung Pleural
Hashimoto 2016 [23]	1	F	72	7.7	N	8–10	I	1.25	A	N
The present Case 2023	1	M	76	4.7	Y	4–6	IIB	1	A	N

M: Male F: Female A: Alive D: Die NA: Not Available Y: Yes N: No

the histological subtype. In the present case, chest CT revealed the presence of a mass with expansive growth, a well-demarcated border, and a lack of invasion into surrounding structures, which seemed to indicate a benign nature. However, atypical type A thymoma was diagnosed postoperatively. This suggests that imaging modalities have a limited ability to predict the biological behaviour of such tumours. Zhao et al. reported that ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT may assist in predicting the grade of thymic epithelial malignancies, as they found that the maximum standardised uptake value (SUVmax) and SUVmax/tumour size significantly correlated with the WHO histological classification of thymic epithelial tumours [8]. SUVmax may be higher in primary and metastatic atypical type A thymomas than in classical type A thymomas. This suggests that 18F-FDG PET/CT imaging may be able to predict the biological behaviour of such tumours.

Pathology has shown that the majority of atypical type A thymomas possess a capsule. Maximum tumour diameters were in the range of 2.6–13 cm and had an average value of 7 cm. Cystic changes and necrosis may be present on the cut surface; solid areas may appear lobulated; and infiltration of surrounding tissues is commonly present. Compared to type A thymomas, atypical type A thymomas had a greater abundance of tumour cells and exhibited mild atypia. Neoplastic coagulative necrosis was commonly present (7/15, 46.6%). Cytoplasm was scant and pale-staining, and nuclei were short, spindle-shaped or oval-shaped, had deeply stained chromatin, and contained inconspicuous nucleoli.

Classic type A thymomas have low mitotic activity, with counts usually < 4 mitoses /10HPFs. According to the reported literature, 91.7% (11/12)of cases had mitotic activity ≥ 4 mitoses/10HPFs.

The immunophenotype of atypical type A thymomas was similar to that of type A thymomas. In 2014, the International Thymic Malignancy Interest Group proposed that epithelial expression of CD20 is a potential marker for type A thymomas, but this is infrequently present in atypical type A thymomas [4]. However, our data show that CD20 expression is present in 46.7% (7/15)of atypical type A thymomas, suggesting that CD20 has no differentiating significance in type A thymomas and atypical type A thymomas. Montpréville et al. observed strong regional expression of Glut-1 in a case of atypical type A thymoma and extremely weak Glut-1 expression in four cases of type A thymoma, demonstrating that Glut-1 expression may also form a basis for differentiating between these two thymoma types [9]. It is widely recognised that Ki67 is a cell proliferation marker that is also associated with tumour aggressiveness. Roden et al. reported that tumours with a Ki-67 labelling index

(LI) ≥ 13.5% were thymic carcinomas, those with a Ki-67 LI < 2.0% were type A thymomas, and those with Ki-67 LI values of 2–13.5% could not be definitively classified [10]. In the present case, the Ki67 LI value in the hot spot region was 15%, suggesting that the aggressiveness of atypical type A thymomas may be similar to that of thymic carcinomas.

The differential diagnosis of atypical type A thymoma by histology mainly included spindle cell type B3 thymoma and (spindle cell) thymoma carcinoma. Prominent and abundant perivascular spaces would strongly favor a diagnosis of type B3 thymoma, whereas uniform nuclei, abundance of capillary vessels, cystic spaces, rosette formation, and epithelial expression of CD20 would favor type A thymoma. Nevertheless, distinction between atypical type A thymoma and (spindle cell) thymoma carcinoma can be more difficult. Atypical type A thymoma usually shows low-grade nuclear atypia, is CD20-positive, and may harbour rare TdT-positive immature T cells.

Follow-up of the 15 reported cases in the literature revealed that 14 patients were still alive (2 months–15 years) and that one had died (15 years) during the follow-up period. Metastasis occurred in ten patients during this period, of whom eight experienced lung metastases (with one case also having concurrent brain metastases, One case with pleural invasion) and two experienced bone metastases.Of the 10 cases with metastasis, 5 were accompanied by necrosis, 3 were not accompanied by necrosis, and 2 were unclear. Vladislav et al. reported that necrosis was the only factor correlated with postoperative relapse and metastases in atypical type A thymomas, whereas tumour size, nuclear morphology, and mitotic activity were not associated with outcome parameters. They also found that surgical margin status was not significantly correlated with relapse or metastases [2]. Gerrn et al. found the concept of more aggressive atypical variants in type A and type AB thymomas. However, only necrosis was significantly associated with advanced stages [11]. According to our data analysis, cases with necrosis stage later and have a higher probability of metastasis. Kawagishi et al. recently reported a case of small-sized (12 mm) type A thymoma with pulmonary metastasis in which increased mitotic counts and focal necrosis were not observed, demonstrating that clinical aggressiveness is not always associated with atypicality [1].

Certain correlations may exist between the clinical behaviour and molecular characteristics of tumours. A study by Wells et al. discovered that the most frequent somatic mutation in thymomas was the nucleotide hotspot mutation c.1271T > A p. (L424H) in GTF2I [12]. This mutation has been found in 78.6% and 83.9% of type A and type AB thymomas, respectively, but rarely occurs in other thymomas and thymic carcinomas. In addition, the GTF2I mutation has been found to be uniquely correlated with spindle-cell morphology in type A and type AB thymomas, including thymomas with atypical features and the micronodular type. The researchers concluded that the presence of GTF2I mutations is associated with early Masaoka stage and good prognosis.Grajkowska et al. described a case of AB thymoma with an atypical type A component, the GTF2I mutation was detected for the first time in both primary and metastatic tumors [13]. However, the patient developed lung and brain metastases and died after 10 and 15 years, suggesting that the presence of GTF2I mutations does not necessarily have a good prognosis. So far, molecular biology studies on atypical type A thymoma have not yet identified specific changes.

The pathogenesis of atypical type A thymoma remains unclear. Yanagiya et al. reported that atypical and typical type A regions were adjacent and deduced that atypical type A thymomas may have developed from type A thymomas [14]. A study by Shen et al. found two cases of atypical type A thymoma contiguous with a multilocular thymic cyst (MTC), indicating that atypical type A thymomas and type A thymomas may arise from MTCs and that a histogenetic link may exist between MTCs and thymic tumours [15]. Daisuke et al. showed atypical type A thymoma was a bridge between con ventional type A thymoma and spindle cell thymic car cinoma. In other words, they tentatively view them as the spindle cell counterparts of B3 thymomas [16]. From the clinical manifestation, Yanagiya et al. found that atypical type A thymoma may be associated with autoimmune disease [17]. However, in the present case, classical type A thymoma areas, transitional zones, or thymic cysts were not found upon adequate sampling of the tumour, and also no clinical evidence of autoimmune disease, resulting in our inability to corroborate the above viewpoints. Therefore, further case studies are required to elucidate the pathogenic mechanisms of this disease.

In summary, we reported a rare case of atypical type A thymoma. Given the limited number of cases, there is a relative lack of research on the histological features, pathogenesis, and molecular changes of atypical type A thymomas. Further data accumulation is required to gain deeper insight into these rare neoplasms. It should be noted that atypical thymomas usually exhibit a focal distribution of lesions and that inadequate sampling or a lack of thoroughness in image reading may lead to missed diagnoses. atypical type A thymoma should be suspected when the tumor has one or more of the following pathologic features: hypercellularity, increased mitotic count(≥4 mitoses/10HPFs), and focal necrosis.Therefore, clinicians should exercise extra caution and vigilance during their daily diagnostic work.

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Author contributions
Liling Qin† and Fanrong Wang† contributed equally to this work. Conceptualization: Ning Zhou, Liling Qin. Data curation: Liling Qin, Fanrong Wang, Liqiao Chen, Tao Li, Gang Wang. Immunohistochemical staining analysis: Liqiao Chen, Tao Li. Histologic diagnosis: Liling Qin, Ning Zhou. Writing – original draft: Liling Qin and Fanrong Wang. Writing – review & editing: Liqiao Chen, Tao Li, Gang Wang, Ning Zhou. All authors contributed to the writing of the paper and approved the fnal version for publication.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to aprticipate
For this study, photos, and writing of our manuscript, the patient or the patient's parents have given their written informed consent. This study was approved by the ethics committee of Sichuan Mianyang 404 Hospital.

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