Dear editor

We sincerely thank the editor and all reviewers for their valuable feedback that we have used to improve the quality of our manuscript. According to your nice suggestions, we have made some corrections to our manuscript, the detailed corrections are listed below.

1, Page 3, “Case presentation”. In the presentation of the case, a paragraph explaining the histopathological method is missing: what fixative was used? How was the organ fragment (paraffin, I assume) embedded? A few words regarding the dehydration, rehydration and staining steps would have been helpful.

We added an explanation of the histopathological approach. Page 4, line 145.

2. For the different imaging methods (colour Doppler ultrasonography, computed tomography), some details on the models of devices used would also be useful.

The models of ultrasound and ct equipment we have labelled in the text. Page 4, line 137.

3. Page 4, line 113. Separate Figures 1 and 2 with their appropriate legends below each. Figure 1: give some explanation about the figure. Use arrows to show the lesions on the figure. Use letters to indicate the different parts of the organs. Add a scale bar on the image. Figure 2: same: give some explanation about the figure. Use arrows to show important parts in the figure. Use letters to indicate the different parts of the organs. Add a scale bar on the image. Figure 2 is not called in the text. Page 4, line 119 Separate Figures 3 and 4 with their appropriate legends below each. Figure 5: use arrow to show the gel-like cut of the mass. Page 5, figures 5 and 6: Separate Figures 5 and 6 with their appropriate legends below each. For both figures:
indicate the different parts observed on the sections on each figure.
We have rearranged the images and explained them at the bottom.

Thank you again for your kindness and patience.

Best regards

Ying Liu

Aggressive angiomyxoma of the epididymis: A case report and literature review

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Data Availability Statement
The datasets used during the current study are available from the corresponding author upon reasonable request.

Abstract

BACKGROUND
Aggressive angiomyolipoma is an extremely rare benign mesenchymal tumor that was originally described as a locally recurrent mucinous spindle cell tumour. Aggressive angiomyolipoma originates from myofibroblasts, vascular
smooth muscle cells, or fibroblasts, and displays various phenotypes of myofibroblasts and abnormal muscle arteries. Aggressive angiomyolipoma was first identified in 1983 and fewer than 50 male patients have been reported to date. It is an extremely rare mesenchymal tumour and often confused with other diseases. Patients with epididymal Aggressive angiomyolipoma lack typical symptoms, most of which occur incidentally, although some patients may experience mild pain, discomfort, and swelling. Pain may be exacerbated by pressure from the mass.

**CASE SUMMARY**

A 66-year-old male was admitted to the hospital on January 14 2022 with chief complaint of swelling in the left scrotum for one year. There was no apparent cause for the swelling. The patient did not consult with any doctor or receive any treatment for the swelling. The enlarged scrotum increased in size gradually until it reached approximately the size of a goose egg, and was accompanied by discomfort and swelling of the left cavity of the scrotum. The patient had no history of any testicular trauma, infection, or urinary tract infection (UTI). The patient urinated freely, 1–2 times at night, without urgency, dysuria (painful urination), or haematuria. There was no significant family history of malignancy. The patient underwent excision of the enlarged tumour and the left epididymis under general anaesthesia on January 18 2022. Twelve months of follow-up revealed no recurrence. The patient was satisfied with the treatment.

**CONCLUSION**

Aggressive angiomyolipoma is extremely rare clinically and often confused with other diseases. The pathogenesis of aggressive angiomyolipoma is unclear and the clinical presentation is mostly a painless enlarged mass. The diagnosis of aggressive angiomyolipoma requires a combination of medical history, preoperative imaging such as computed tomography (CT) and magnetic resonance imaging (MRI), cytological examination and preoperative and postoperative pathological biopsy. The preferred treatment is surgery, with the
possibility of a new alternative treatment option after hormonal therapy. Aggressive angiomyolipoma should be considered in the differential diagnosis of parametrial tumors of the male genital area that present as clinically significant masses. The high recurrence rate of aggressive angiomyolipoma may be related to incomplete tumor resection, and patients with aggressive angiomyolipoma are advised to undergo annual postoperative follow-up and imaging for recurrence.

Keywords: Aggressive angiomyxoma; Mesenchymal tumor; Scrotal mass; Epididymal malignancy; Orchiectomy; Male reproductive system neoplasms

1 Introduction

Aggressive angiomyxoma is a benign mesenchymal tumour that was originally described as a locally recurrent mucinous spindle cell tumour originating mainly in the soft tissues of the pelvic region of premenopausal women (1). The mean age of onset of aggressive angiomyolipoma in male patients is approximately 46 years (range: 1–82 years) (2). Aggressive angiomyolipoma was first identified in 1983 and fewer than 50 male patients have been reported to date (3). Of these, 38%, 33%, 13%, 8%, and 8% of the cases involved the scrotum, spermatic cord, perineum, pelvic organs, and bladder, respectively (4). Intrascrotal aggressive angiomyolipoma is frequently misdiagnosed on physical examination, similar to other urological conditions, such as testicular tumours, varicocele, and inguinal hernia. Patients with epididymal aggressive angiomyolipoma lack typical symptoms, most of which occur incidentally, although some patients may experience mild pain, discomfort, and swelling. Pain may be aggravated by mass pressure. Aggressive angiomyolipomas grow rapidly in an infiltrative manner with poorly defined borders, vary in size, and often adhere to the testis. When a tumour infiltrates the spermatic cord, symptoms of spermatic cord thickening may be observed. Furthermore scrotal ultrasonography reveals only hypoechoic or cystic masses with vascularity, making it difficult to distinguish aggressive angiomyolipoma from other mesenchymal tumours.
2 Case presentation

Chief complaints
The patient, male, 66 years old, was admitted to the hospital with a left scrotal mass that had been there for one year.

History of present illness
A 66-year-old male was admitted to the hospital on January 14, 2022 presenting with a year-long finding of left scrotal swelling with no apparent cause. The swelling was approximately the size of an egg, without any discomfort. Later, the scrotal swelling increased gradually and was approximately the size of a goose egg, accompanied by discomfort in the left cavity of the scrotum. The patient had no history of testicular trauma, sexually transmitted diseases, UTI, undescended testes, or groin/scrotal surgery.

History of past illness
The patient had no pertinent past illness history.

Personal and family history
The patient had no pertinent personal or family history.

Physical examination
On physical examination, the vital signs were as follows: Body temperature, 36.2 °C; blood pressure, 140/80 mmHg; heart rate, 64 beats per min; respiratory rate, 20 breaths per min. The penis was of the adult type. There was a solid and tough swelling (size: approximately 12.0×9.0 cm) in the left cavity of the scrotum. The left testicle and epididymis were not palpable, whereas the right testicle and epididymis were not nodular and painful to palpation.

Laboratory examinations
The following blood tests were performed: Liver function, renal function, serum electrolytes, thyroid function, coagulopathy, markers of myocardial injury, syphilis, HIV, glycosylated hemoglobin, lipids, rheumatoid factor, erythrocyte sedimentation rate, immune panel, and tumor markers. All laboratory values were within reference ranges.

Imaging examinations
Computed tomography (CT,Philis EPIQ5,USA) showed a cystic lesion in the left scrotum measuring approximately 6.6×5.5 cm (Figure 1). Colour Doppler ultrasonography (SOMATOM Definition Flash,Siemens, Germany) revealed a hypoechoic mass in the left scrotum(Figure 2). Further imaging examinations, including whole-abdomen CT and bone scans, did not reveal lymph node enlargement or distant tumour metastasis. The tumour markers lactate dehydrogenase, β-human chorionic gonadotropin, α-fetoprotein, and CEA were at normal levels.

**Pathological examination**

Postoperative tumour tissues were fixed with 4% paraformaldehyde and embedded in paraffin for Hematoxylin-eosin (H&E) staining and immunohistochemistry (IHC). Tissue sections were deparaffinized in xylene, dehydrated in graded ethanols and finally hydrated in distilled water, the sections were then counterstained with HE. IHC was performed using antibodies directed against vimentin, cytokeratin (CK), desmin, S-100 protein, SMA,CD68, Bcl-2,CD31, P53 and Ki-67.
**Figure 1** Computed tomography: The CT showed a cystic lesion in the left scrotum measuring about 6.6*5.5 cm with clear borders (red arrow), and the left testicle was normal in size (white arrow).

**Figure 2** Colour Doppler ultrasonography (Testes, epididymis and spermatic cord): Ultrasound showed that the left testicle size was 4.3×2.8×2.6 cm (white arrow). On the left side of the scrotum there was a well-defined hypoechoic mass (red arrow) with regular morphology and heterogeneous internal echogenicity.
Figure 3 Gross pathological picture of this case of epididymal mucinous neoplasm. The visible mass is an enveloped, white, grey, well-confined solid tumour (7.0×6.0 cm)
Figure 4 A gel-like cut of the mass can be seen (red arrow).

**TREATMENT**

The patient underwent excision of the enlarged tumour and the left epididymis under general anaesthesia on January 18 2022.

**OUTCOME AND FOLLOW-UP**
Intraoperatively, adhesions were found between the inner and outer fascia of the spermatic cord and the sheath layer, and the testis was observed to be atrophied when the sheath was incised. The head and body of the epididymis were normal in shape, and a mass measuring approximately 10 cm with a heterogeneous texture at the tail of the epididymis was observed. The size of the left paratesticular mass was approximately 70×70×60 mm (Figure 3), with an envelope and a greyish-red, greyish-yellow, translucent cut surface (Figure 4), and the spermatic cord. The swelling was 17×10×10mm, with greyish white cut surface and medium texture.

Two oval-shaped masses along the edges of the scrotal and epididymal masses and the white membrane of the testis were removed gradually. Swelling below the testes was selected for intraoperative freezing.

Postoperative pathology revealed a mesenchymal tumour that was mucinous in origin. Microscopic examination revealed various tumour cell morphologies, including round or ovoid nuclei, deep staining, eosinophilic cytoplasm, tennis racket-like or spider-like tumour cells, and a variable number of multinucleated giant cells with deep-stained nuclei and lax interstitium. Immunohistochemical results revealed the tumor cells were positive for Vimentin, desmin, CD68 (individual cells), CD31 (vascular), P53 (individual cells), while negative for S-100, SMA, Bcl-2. The Ki-67 index was less than 10%. Combined hematoxylin-eosin staining (HE) and immunophenotype analyses indicated mucinous spindle cell tumour-aggressive angiomucinous tumours (Figures 5 and 6). Twelve months of follow-up revealed no recurrence. The patient was satisfied with the treatment.
Figure 5 Micropathological image of an epididymal mucocele in this case: dilated, thick-walled, hyalinised blood vessels of variable size are seen microscopically (red arrow). H & E, Hematoxylin-eosin; IHC, immunohistochemistry (original magnification of ×200)

Figure 6 Micropathological image of an epididymal mucocele in this case: Clostridial and astrocytic tumour cells (red arrow) were scattered in the mucus stroma with no evident heterogeneity. H & E, Hematoxylin-eosin; IHC, immunohistochemistry (original magnification of ×200)

3 Discussion
Aggressive angiomyolipoma is an extremely rare mesenchymal tumor, and
most patients are women of childbearing age. To date, fewer than 50 cases of aggressive angiomyolipoma have been reported worldwide in men, of which 38%, 33%, 13%, 8%, and 8% are from the scrotum, spermatic cord, perineum, pelvic organs, and bladder, respectively. However, the pathogenesis of aggressive angiomyolipoma is unknown. Intrascrotal aggressive angiomyolipoma is frequently misdiagnosed on physical examination as other urological disorders, such as testicular tumours, varicocele, and inguinal hernia, and has certain characteristic presentations on CT, MRI, and other imaging studies (2). On CT, the tumour shows well-defined borders and no muscle-like tapering. Magnetic resonance imaging and CT angiography are the most effective radiological methods for diagnosing aggressive angiomyolipoma, and T2-weighted MRI reveals tumours with high signal intensity. These manifestations may be related to the sparse mucinous-like stroma and high water content of vascular mucinous tumours [7]. The distinctive "swirling" appearance of the fibromuscular layer can also be detected after contrast injection. A spiral or layered internal structure of the tumour is observed in most patients, which is a typical MRI feature of aggressive angiomyolipoma (a swirling chain aligned with the cranioventral axis). Additionally, CT and MR imaging can accurately show the extension of these tumours over the pelvic diaphragm, which is valuable in determining the surgical pathway.

Aggressive angiomyolipoma exhibits certain characteristic manifestations on CT, MRI, and other imaging modalities. On CT, the boundaries of the tumour are clear, and there is no muscle-like gradual decay-like appearance. Magnetic resonance imaging and CT with contrast are the most effective radiological methods for diagnosing aggressive angiomyolipoma, and T2-weighted MRI reveals tumours with a high signal intensity. These manifestations may be related to the sparse mucinous-like stroma and high water content of vascular mucinous tumours (5). The distinctive "swirling" appearance of the fibromuscular stroma can also be detected after contrast injection. The internal structure of the tumour is spiral or layered in most patients, which is a typical
MRI feature of aggressive angiomyolipoma: a swirling chain aligned with the craniocaudal axis. CT and MR imaging can also accurately demonstrate the extension of these tumours over the pelvic diaphragm, which can be valuable for determining the surgical pathway.

There are no specific tumour markers for aggressive angiomyolipoma. The thick-walled vessels are the main microscopic features of aggressive angiomyolipoma, compared to those of other connective tissue tumours (6). Immunohistochemical studies showed strong positivity for vimentin, smooth muscle actin, and CD34 in the spindle and stellate tumour cells in all cases. Stromal cells were positive for waveform proteins and tumour cells were mostly negative for factor VIII-associated antigen, carcinoembryonic antigen, and cytokeratin (7). Some patients with aggressive angiomyolipoma are positive for desmin, oestrogen receptors, and progesterone receptors, whereas all patients are negative for S-100 (2). In contrast, the significance of the immunohistochemical markers MDM2 and CDK4 (cell cycle protein-dependent kinase 4) is uncertain; MDM2 and CDK4 genes are located on either side of the 12q13-15 region, spanning the HMGA2 locus, and has been suggested to be associated with mutations in chromosomal region 12q13-15 (2, 8). 12q13-15, the most common gene in aggressive angiomyolipoma, is a region that is rearranged in several mesenchymal tumours (8). CDK4 amplification may also contribute to cell cycle progression. Highly proliferative cell nuclear antigens and a lack of p21 protein expression may be associated with an increased propensity for relapse (9).

Aggressive angiomyolipoma diagnosis requires a combination of history, preoperative imaging (such as CT and MRI), cytology, and preoperative and postoperative pathological biopsies. Several other entities in the differential diagnosis of aggressive angiomyolipoma also have a myofibroblastic origin with similar immunohistochemical features (1, 7, 10).

Surgical resection is the first-line of treatment for aggressive angiomyolipoma (4, 5, 8). The high recurrence rate of aggressive angiomyolipoma is likely
related to incomplete tumour resection (11). Therefore, it is important to
determine whether a tumour is primary or metastatic before surgery. Generally,
aggressive angiomucinous tumours do not metastasise distally. To date, no
metastatic tumours have been reported in men, whereas cases of metastasis
have been reported in women. The first metastasis of aggressive
angiomyolipoma usually occurs in the pelvis, followed by extensive
dissemination in the lung, mediastinal, iliac, and aortic lymph nodes with
peritoneal dissemination, and the patient eventually dies due to multiple organ
failure (12). Therefore, annual postoperative follow-ups and imaging for
recurrence are recommended in patients with aggressive angiomyolipoma (13).
Radiotherapy can be used as a hormonal therapy or to control multiple
recurrences after surgical resection with poor results (14). Furthermore,
radiotherapy is ineffective in the treatment of aggressive angiomyolipoma
because of the slow progression of the disease (15). Hormonal therapies, such
as GnRH-a (goserelin), or other antiestrogen drugs (tamoxifen) are novel
alternatives to pharmacotherapy (16-19). The localization and growth of
aggressive angiomyolipoma are limited to the genital region and may be
associated with sex hormones, especially oestrogen in women and androgens
in men. Relevant studies have suggested that the growth of aggressive
angiomucinous tumours in men may be associated with androgens, whereas
the tumour tissues of female patients are usually strongly positive for oestrogen
receptor (ER) and progesterone receptor (PR) and those in men are usually
negative for ER and PR staining (1). A 37-year-old woman with aggressive
angiomyolipomas was reported. Immunohistochemistry showed ER and PR
positive. She received GnRH-a drug for 6 courses and was followed up for 3
years without recurrence(20). However, long-term treatment with GnRH
agonists may induce some side effects, such as osteoporosis and depression, so
the optimal treatment regimen for GnRH agonists needs further study.

5  Conclusion

Aggressive angiomyolipomas of the epididymis are rare and often
misdiagnosed. Their pathogenesis is unclear, and clinical presentation in most cases is a painless, enlarged mass. Aggressive angiomyolipoma diagnosis requires a combination of medical history, preoperative imaging (such as CT and MRI), cytological examination, and preoperative and postoperative pathological biopsy. Surgery is the preferred treatment option, with the possibility of a new alternative after hormonal therapy. Aggressive angiomyolipoma should be considered in the differential diagnosis of parametrial tumours of male genital area that present as clinically significant masses.

6 Acknowledgments
The authors would like to thank Editage (www.editage.cn) for English language editing.

7 Abbreviations
UTI Urinary tract infection
CEA Carcinoembryonic antigen
CT Computed tomography
MRI Magnetic resonance imaging

8 Author Contributions
XJL and JHS wrote the main manuscript. QZF prepared Figs Figs1, 2, 3, 4, 5, 6. YL revised the final manuscript. All the authors have read and approved the final manuscript.

9 Funding
None

10 Availability of data and materials
The datasets used during the current study are available from the corresponding author upon reasonable request.

11 Declarations
Ethics approval and consent to participate
This case report was approved by the Ethics Committee of the Affiliated Zhongshan Hospital of Dalian University. Written informed consent was obtained from the patient for publication of this clinical case report.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests
The authors declare no competing interests.

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