MINIREVIEWS

6974 Applications of time series analysis in epidemiology: Literature review and our experience during COVID-19 pandemic
Tomov L, Chervenkov L, Miteva DG, Batselova H, Velikova T

ORIGINAL ARTICLE

Retrospective Cohort Study

6984 Acute cholangitis: Does malignant biliary obstruction vs choledocholithiasis etiology change the clinical presentation and outcomes?
Tsou YK, Su YT, Lin CH, Liu NJ

Retrospective Study

6995 Usefulness of analyzing endoscopic features in identifying the colorectal serrated sessile lesions with and without dysplasia

7004 Roles of biochemistry data, lifestyle, and inflammation in identifying abnormal renal function in old Chinese
Chen CH, Wang CK, Wang CY, Chang CF, Chu TW

7017 Clinical efficacy and safety of Guipi decoction combined with escitalopram oxalate tablets in patients with depression
Yu J, Xu FQ

7026 Artificial intelligence technology and ultrasound-guided nerve block for analgesia in total knee arthroplasty
Tong SX, Li RS, Wang D, Xie XM, Ruan Y, Huang L

7034 Axenfeld-Reiger syndrome: A search for the missing links
Morya AK, Ramesh PV, Sinha S, Nishant P, Nain N, Ramavath RN, Gone C, Prasad R

Observational Study

7043 Self-management of osteoarthritis while waiting for total knee arthroplasty during the COVID-19 pandemic among older Malaysians
Mahdzir ANK, Mat S, Seow SR, Abdul Rani R, Che Hasan MK, Mohamad Yahaya NH

7053 “In situ” bone flap” combined with vascular pedicled mucous flap to reconstruction of skull base defect

7061 Reference values of gait parameters in healthy Chinese university students: A cross-sectional observational study
## Contents

**Thrice Monthly Volume 11 Number 29 October 16, 2023**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7075</td>
<td>Effect of T-regulatory cells and interleukin-35, interleukin-10, and transforming growth factor-beta on diffuse large B-cell lymphoma</td>
<td>Wu H, Sun HC, Ouyang GF</td>
</tr>
<tr>
<td>7082</td>
<td>META-ANALYSIS</td>
<td></td>
</tr>
<tr>
<td>7091</td>
<td>CASE REPORT</td>
<td></td>
</tr>
<tr>
<td>7091</td>
<td>Meta-analysis of the efficacy and safety of daratumumab in the treatment of multiple myeloma</td>
<td>Wang P, Jin SY</td>
</tr>
<tr>
<td>7101</td>
<td>Varicella-zoster virus meningitis with hypoglycorrachia: A case report</td>
<td>Cao LJ, Zheng YM, Li F, Hao HJ, Gao F</td>
</tr>
<tr>
<td>7107</td>
<td>Unusual presentation of penile giant condyloma acuminatum with spontaneous prepuce perforation: A case report</td>
<td>Hsu FC, Yu DS, Pu TW, Wu MJ, Meng E</td>
</tr>
<tr>
<td>7113</td>
<td>Primary renal lymphoma presenting as renal failure: A case report and review of literature from 1989</td>
<td>Lee SB, Yoon YM, Hong R</td>
</tr>
<tr>
<td>7136</td>
<td>Mucoepidermoid carcinoma of the lung with hemoptysis as initial symptom: A case report</td>
<td>Xie WX, Liu R, Li Z, Zhou PL, Duan LN, Fu DD</td>
</tr>
<tr>
<td>7144</td>
<td>Co-infection of <em>Chlamydia psittaci</em> and <em>Tropheryma whippeli</em>: A case report</td>
<td>Du ZM, Chen P</td>
</tr>
<tr>
<td>7150</td>
<td>Surgical treatment of severe anterior capsular organized hard core cataract: A case report</td>
<td>Wang LW, Fang SF</td>
</tr>
<tr>
<td>7156</td>
<td>First platelet transfusion refractoriness in a patient with acute myelocytic leukemia: A case report</td>
<td>Tu SK, Fan HJ, Shi ZW, Li XL, Li M, Song K</td>
</tr>
<tr>
<td>7162</td>
<td>Rare finding of primary aortoduodenal fistula on single-photon emission computed tomography/computed tomography of gastrointestinal bleeding: A case report</td>
<td>Kuo CL, Chen CF, Su WK, Yang RH, Chang YH</td>
</tr>
<tr>
<td>7170</td>
<td>Rituximab combined with Bruton tyrosine kinase inhibitor to treat elderly diffuse large B-cell lymphoma patients: Two case reports</td>
<td>Zhang CJ, Zhao ML</td>
</tr>
</tbody>
</table>
## Contents

**Thrice Monthly Volume 11 Number 29 October 16, 2023**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7179</td>
<td>Use of Ilizarov technique for bilateral knees flexion contracture in Juvenile-onset ankylosing spondylitis: A case report</td>
<td>Xia LW, Xu C, Huang JH</td>
</tr>
<tr>
<td>7187</td>
<td>Case of takotsubo cardiomyopathy after surgical treatment of liver hydatid cyst: A case report</td>
<td>Altas Y, Abdullayeva Ü</td>
</tr>
<tr>
<td>7193</td>
<td>Laparoscopic cholecystectomy and transduodenal T-tube insertion with indocyanine green fluorescence imaging and laparoscopic ultrasound: A case report</td>
<td>Yoo D</td>
</tr>
<tr>
<td>7200</td>
<td>Hematopoietic stem cell transplantation of aplastic anemia by relative with mutations and normal telomere length: A case report</td>
<td>Yan J, Jin T, Wang L</td>
</tr>
<tr>
<td>7207</td>
<td>Emphysematous thrombophlebitis caused by a misplaced central venous catheter: A case report</td>
<td>Chen N, Chen JJ, Chen T, Zhang W, Fu XY, Xing Z</td>
</tr>
<tr>
<td>7214</td>
<td>Aggressive angiomyxoma of the epididymis: A case report</td>
<td>Liu XI, Su JH, Fu QZ, Liu Y</td>
</tr>
<tr>
<td>7221</td>
<td>Gastric and intestinal ectopic pancreas: Two case reports</td>
<td>Zhang H, Zhao HY, Zhang FH, Liang W</td>
</tr>
<tr>
<td>7234</td>
<td>Imaging misdiagnosis and clinical analysis of significant hepatic atrophy after bilioenteric anastomosis: A case report</td>
<td>Liang SY, Lu JG, Wang ZD</td>
</tr>
<tr>
<td>7248</td>
<td>Simultaneous thyroglossal duct cyst with parathyroid cyst: A case report</td>
<td>Chen GY, Li T</td>
</tr>
<tr>
<td>7253</td>
<td>Submandibular solid-cystic mass as the first and sole manifestation of occult thyroid papillary carcinoma: A case report</td>
<td>Chen GY, Li T</td>
</tr>
</tbody>
</table>

**LETTER TO THE EDITOR**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7258</td>
<td>Artificial intelligence and machine learning in motor recovery: A rehabilitation medicine perspective</td>
<td>Swarnakar R, Yadav SL</td>
</tr>
</tbody>
</table>
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Aggressive angiomyxoma of the epididymis: A case report

Xu-Jie Liu, Jia-Hao Su, Qi-Zhong Fu, Ying Liu

BACKGROUND
Aggressive angiomyxoma is an extremely rare benign mesenchymal tumor that was originally described as a locally recurrent mucinous spindle cell tumour. Aggressive angiomyxoma originates from myofibroblasts, vascular smooth muscle cells, or fibroblasts, and displays various phenotypes of myofibroblasts and abnormal muscle arteries. Aggressive angiomyxoma 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 angiomyxoma 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. 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 angiomyxoma is extremely rare clinically and often confused with other diseases. The pathogenesis of aggressive angiomyxoma is unclear and the clinical presentation is mostly a painless enlarged mass. The diagnosis of aggressive angiomyxoma requires a combination of medical history, preoperative imaging such as computed tomography and magnetic resonance imaging, cytolo-
Aggressive angiomyxoma of the epididymis

INTRODUCTION

Aggressive angiomyxoma is a benign mesenchymal tumor that was originally described as a locally recurrent mucinous spindle cell tumor 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 tumors, 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 tumor 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 tumors.

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, urinary tract infection, 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/min; respiratory rate, 20 breaths/min. The penis was of the adult type. There was a solid and tough swelling (size: Approximately 12.0 cm × 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, human immunodeficiency virus, 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, United States) showed a cystic lesion in the left scrotum measuring approximately 6.6 cm × 5.5 cm (Figure 1A). Colour Doppler ultrasonography (SOMATOM Definition Flash, Siemens, Germany) revealed a hypoechoic mass in the left scrotum (Figure 1B). 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 carcinoembryonic antigen were at normal levels.

**FINAL DIAGNOSIS**

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 2A and B). Twelve months of follow-up revealed no recurrence. The patient was satisfied with the treatment.

**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 mm × 70 mm × 60 mm (Figure 3A), with an envelope and a greyish-red, greyish-yellow, translucent cut surface (Figure 3B), and the spermatic cord. The swelling was 17 mm × 10 mm × 10 mm, 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 HE and immunophenotype analyses indicated mucinous spindle cell tumour-aggressive angiomucinous tumours (Figures 2A and B). Twelve months of follow-up revealed no recurrence. The patient was satisfied with the treatment.
Figure 1 Computed tomography and colour Doppler ultrasonography (testes, epididymis and spermatic cord). A: The computed tomography showed a cystic lesion in the left scrotum measuring about 6.6 cm × 5.5 cm with clear borders (orange arrow), and the left testicle was normal in size (white arrow); B: Ultrasound showed that the left testicle size was 4.3 cm × 2.8 cm × 2.6 cm (white arrow). On the left side of the scrotum there was a well-defined hypoechoic mass (orange arrow) with regular morphology and heterogeneous internal echogenicity.

Figure 2 Micropathological image of an epididymal mucocele in this case. A: Dilated, thick-walled, hyalinised blood vessels of variable size are seen microscopically (orange arrow); B: Clostridial and astrocytic tumour cells (orange arrow) were scattered in the mucus stroma with no evident heterogeneity. Original magnification of × 200.

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, magnetic resonance imaging (MRI), and other imaging studies[2]. On CT, the tumour shows well-defined borders and no muscle-like tapering. MRI 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[5]. 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 MRI can accurately show the extension of these tumours over the pelvic diaphragm, which is valuable in determining the surgical path-way.

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. MRI 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[6]. 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 cranio-caudal axis. CT and MRI 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[7]. 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[6]. Some patients with aggressive angiomyolipoma are positive for desmin, estrogen receptors (ERs), and progesterone receptors (PRs), whereas all patients are negative for S-100[2]. In contrast, the significance of the immunohistochemical markers murine double minute 2 (MDM2) and cell cycle protein-dependent kinase 4 (CDK4) 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[1,5,10].

Surgical resection is the first-line of treatment for aggressive angiomyolipoma[4,6,8]. 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 gonadotropin-releasing hormone agonist (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 ER and 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.

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.

FOOTNOTES

Author contributions: Liu XJ and Su JH contributed equally to this manuscript and can be regarded as co-first authors; Liu XJ and Fu QZ performed the surgery, analysed and collected the data; Liu XJ and Su JH wrote the paper and the study concept and design; Liu Y performed the linguistic review; Liu Y critically reviewed the manuscript; Fu QZ performed the histological analyses, analysed and interpreted the imaging findings; and all the authors provided final approval for the version to be final approval of the submitted version.

Informed consent statement: 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.

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