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Genitourinary

Multiparametric ultrasound findings of tuberculous orchitis following bacillus Calmette-Guérin therapy

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ABSTRACT

Granulomatous bacillus Calmette-Guérin (BCG) infection, both localized and disseminated, as a complication of intravesical therapy for transitional cell carcinoma of the bladder is a recognized but highly unusual phenomenon. We report the case of an 89-year-old gentleman with a history of bladder transitional cell carcinoma and subsequent intravesical BCG instillation of the bladder who presented to his general practitioner with a non-tender lump in his left testis. Histopathologic and microbiological evaluation of the subsequent orchidectomy specimen revealed granuloma formation secondary to BCG infection. The use of bubble contrast agents and elastography in ultrasound to evaluate focal testicular lesions is a relatively novel concept, and we aim to highlight the imaging features of testicular BCG infection using these techniques.

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Case report

An 89-year-old gentleman with a history of abdominal aortic aneurysm (AAA) repair in 2003 had a papillary bladder wall lesion incidentally identified on a routine surveillance scan for his AAA in September 2013. In addition to his AAA, he had a history of ulcerative colitis, hypertension, and hiatus hernia.

The bladder wall lesion was confirmed on flexible cystoscopy, and the patient went on to have a transurethral resection of bladder tumor. Histology demonstrated papillary tumor without deep muscle involvement (T2a N0 M0).

Following discussion at the multidisciplinary meeting, the patient was treated with once-weekly intravesical BCG instillation for 6 weeks starting in December 2013, with maintenance treatment every 6 months. A further 3 instillations were given

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in June 2014. Surveillance cystoscopy 6 months following this did not reveal any evidence of recurrent disease, and the patient was discharged with routine clinic follow-up.

In September 2015, the patient was referred back to urology via his general practitioner to whom he presented with a hard, non-tender testicular lump. He complained of some initial discomfort, although this later disappeared. He denied any urinary symptoms.

A scrotal ultrasound demonstrated a hypoechoic mass in the lower pole of the right testis, measuring $3.0 \times 2.6 \times 2.2$ cm (Figs. 1 and 2) with mildly increased peripheral vascularity on color Doppler imaging but no internal Doppler flow (Fig. 3). No hydroceles or epididymal abnormality was seen, and the left testis was normal. A further ultrasound study 4 weeks later was arranged using a LOGIQ E9 (General Electric) ultrasound machine with dedicated strain elastography software and IV sulfur hexafluoride microbubble for dynamic contrast assessment (4.8 cc of Sonovue).

Strain elastography showed uniformly increased dark-blue color corresponding to increased stiffness in relation to the adjacent normal testicular parenchyma seen in areas of green and red (Fig. 4). A ratio of stiffness was also calculated after regions of interest were drawn, showing the target lesion to be approximately 6 times stiffer than the adjacent normal testicular parenchyma (Fig. 5).

Contrast sonography reflected the increased peripheral vascularity seen on Doppler images to a greater degree and provided additional information with regard to enhancement dynamics, showing early and sustained peripheral contrast uptake but almost no appreciable internal vascularity (Fig. 6).

These initial findings were thought to be in keeping with a necrotic testicular tumor. It was explained to the patient that a testicular tumor at his advanced age would be unusual but could represent lymphoma, and as he was suitable for surgery an orchidectomy was recommended.

Histopathologic examination following surgery revealed prominent granulomatous reaction with caseous necrosis

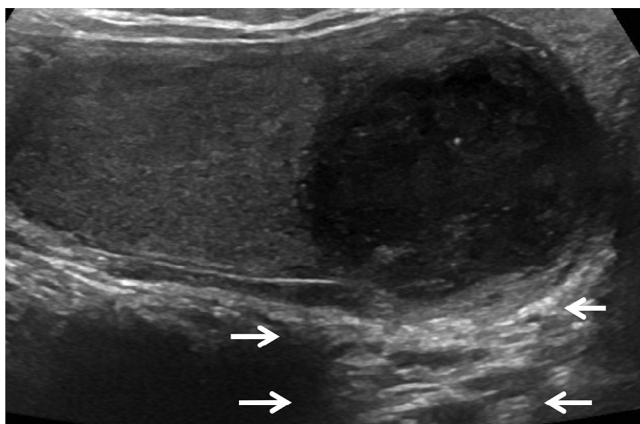


Fig. 1 – Grayscale B-mode ultrasound (sagittal section). Sagittal B-mode image shows a well-defined $3.0 \times 2.6 \times 2.2$ cm hypoechoic lesion in the lower pole of the right testis with posterior acoustic enhancement in keeping with a necrotic center (arrows). The remainder of the right testis is unremarkable.

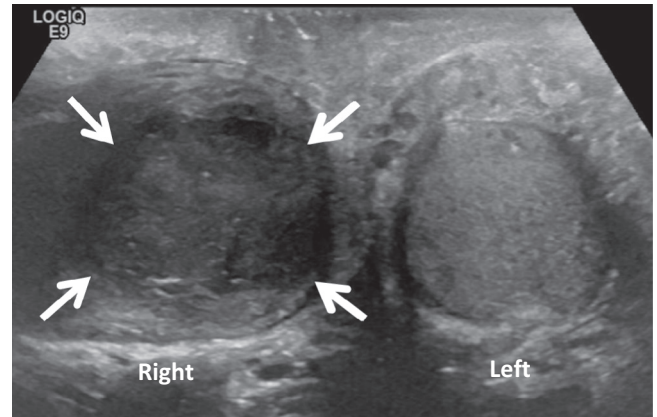


Fig. 2 – Grayscale B-mode ultrasound (transverse section). Transverse B-mode image showing the lower poles of both testes. The abnormal right testis is asymmetrically expanded by the lesion, which is hypoechoic compared with the normal testicular parenchyma seen in the contralateral testis.

(Fig. 7). Langerhans-type multinucleated giant cells were present focally. No evidence of malignancy was seen. Ziehl-Neelsen stains showed acid fast bacilli (Fig. 8) and periodic acid-Schiff stain was negative. The findings were consistent with tuberculous (TB) orchitis. It is important to note that although orchitis was confirmed, there was no imaging or histologic evidence of active concomitant epididymitis.

There was no history of TB contact or exposure, and the patient did not have any clinical symptoms of TB infection. In particular, no respiratory symptoms were present, and chest radiograph was clear. In addition, interferon gamma release assay was negative, suggesting that a diagnosis of latent TB was highly unlikely. All inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were within normal limits. The patient was started on a 6-month course of anti-TB therapy with isoniazid, rifampicin, and pyrazinamide under the care of a respiratory physician, following which he has remained symptom free with regard to TB.

Discussion

BCG (attenuated *Mycobacterium bovis*) therapy has been used to treat bladder cancer since the late 1970s [1]. Although the mechanism of action is uncertain, it is thought that BCG attaches to tumor cells via the glycoprotein fibronectin. The infected urothelial cells induce an immune response through a host of immune mediators including granulocytes, interleukins, macrophages, and tumor necrosis factor. This leads to local inflammation with subsequent host response directed at the affected tissue and eventual tumor eradication [2].

In immunosuppressed patients, BCG can cause infection and induce a granulomatous reaction in affected tissues similar to non-attenuated TB [1]. Although we are not aware of any concomitant acute illness or specific immunosuppressant in his

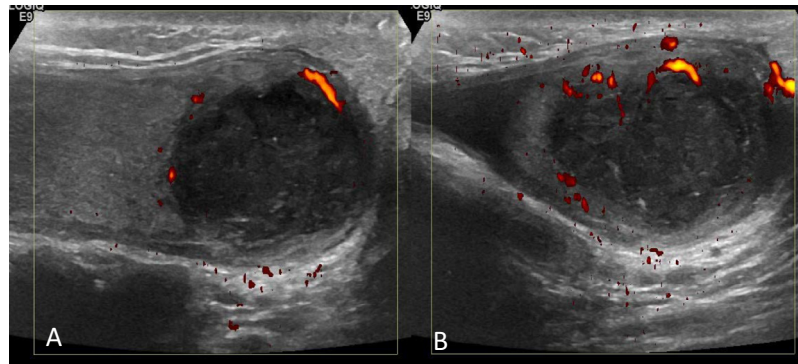


Fig. 3 – Color Doppler ultrasound. Sagittal (A) and axial (B) color Doppler ultrasound image of the lower pole of the right testis, demonstrating that the well-defined hypoechoic lesion has slightly prominent peripheral vascularity but no convincing internal color flow.

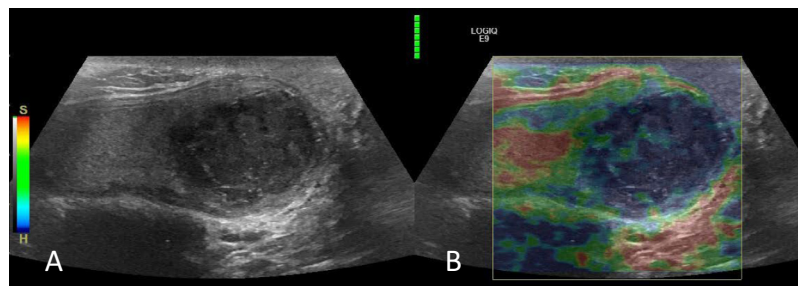


Fig. 4 – Dual-mode strain elastography. Dual-mode strain elastography imaging simultaneously displays the acoustic properties in a standard B-mode image (A) and the elastic properties in an elastogram (B); a color overlay on top of the B-mode image that represents tissue elasticity. As shown in the elastography color bar (left), current practice depicts red regions as tissue that is more elastic (less stiff) than blue regions. This demonstrates that the lesion is harder than the adjacent normal testicular parenchyma.

prescribed medications, the advanced age of our patient may have meant that he was more susceptible to infection.

Granulomatous reactions are a very rare side effect of BCG therapy. A cohort study of 2026 patients conducted by Gonzalez et al. showed that complications of BCG therapy included pneumonitis, hepatitis, mycotic vascular infection, osteomyelitis, and prostatitis, occurring in up to 35 patients [3]. Only

2 of their patients developed orchitis. A similar proportion reported acute-phase symptoms including fever, malaise, weight loss, and nausea, to name a few.

A search of the MEDLINE database using the EBSCO search engine yielded up to 15 previously reported cases of epididymo-orchitis as a complication of intravesical BCG therapy [4–18]. The age range of the patients reported in these articles span

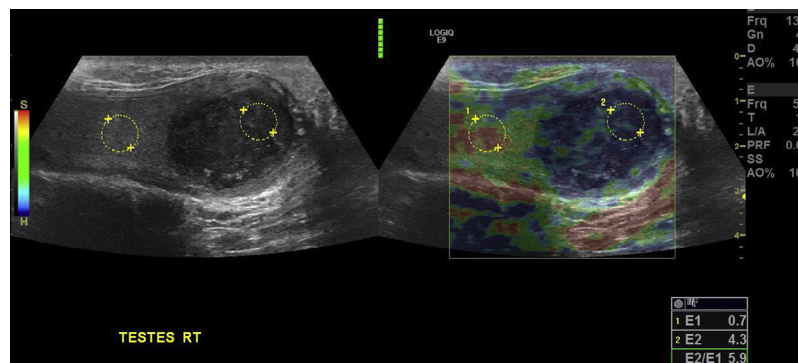


Fig. 5 – Dual-mode elastography with “E-ratio.” Dual-mode strain elastography imaging with “E-ratio” calculation. A circled region of interest (ROI) has been placed on the normal testicular parenchyma (ROI 1) and a second in the lesion (ROI 2) at approximately the same depth. The value $E2/E1 = 5.9$ indicates that the lesion is approximately 6 times stiffer than the normal testicular parenchyma.

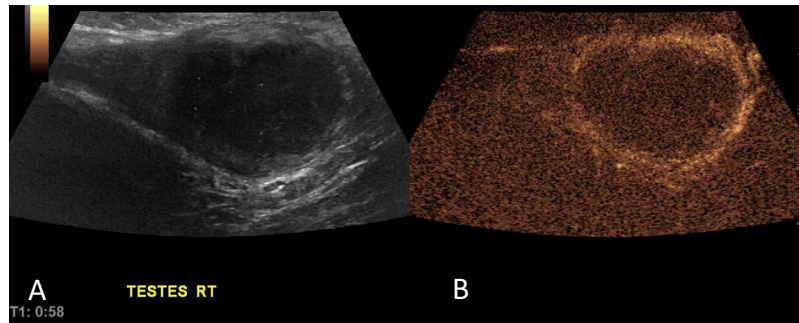


Fig. 6 – Contrast-enhanced ultrasound. Dual split screen still image in contrast mode, with B-mode on the left (A) and contrast window on the right (B), 58 seconds after the injection of 4.8 cc Sonovue contrast followed by a 10 cc bolus of normal saline. This shows peripheral rim enhancement of the lesion with no internal enhancement.

between 54 and 83 years, which makes our patient the oldest reported case of BCG-related orchitis.

Among the abovementioned cases, there is also a large variability in the amount of time between first BCG instillation and onset of orchitis. This varies from 2 months to 17 years in the reported literature although most cases occurred within 2 years of BCG instillation. There are also significant differences in the reported management of these individual cases. All patients underwent orchidectomy. In addition, some received anti-TB medical therapy, whereas others did not. For those patients who received anti-TB medications, some received 4 drug therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide), whereas others received 2 or 3 drugs with variability in the length of treatment ranging between 3 and 9 months.

Although some of the aforementioned papers discuss ultrasound and magnetic resonance imaging findings, our case is the first reported in the literature demonstrating the use of multiparametric ultrasound, that is, B-mode, Doppler, contrast, and elastography in this specific clinical scenario.

Elastography was developed in the 1990s with the aim of mapping structures according to their “stiffness.” The physics behind this is derived from Hooke law, which relates the de-

formation of an object with the force applied to it to calculate the Young modulus of the measured substance. A high Young modulus signifies a high degree of stiffness (low elasticity) and vice versa. Strain elastography requires manual compression of the tissues being scanned. Regions of interest can be specified, and the software will use returned echoes via the transducer to calculate ratios between the target lesion and the adjacent normal tissue to derive elasticity values displayed on a color-scaled map. Strain elastography works well for relatively superficial lesions in the neck, breast, or testes [19]. For deeper lesions, for example in the liver or kidneys, shear wave ultrasound is more appropriate, whereby a mechanical sinusoidal ultrasound wave is applied either in a single fixed burst or intermittently at a fixed frequency compressing the underlying tissues [20].

Contrast sonography involves the intravenous injection of tiny sulfur hexafluoride microbubbles measuring up to a few micrometers in diameter. Tissue perfusion is demonstrated analogous to enhancement seen with contrast in computed tomography or magnetic resonance imaging. Dedicated software relying on pulse inversion techniques is required on the ultrasound equipment to significantly reduce background echoes from the relatively linear surfaces of soft tissue and

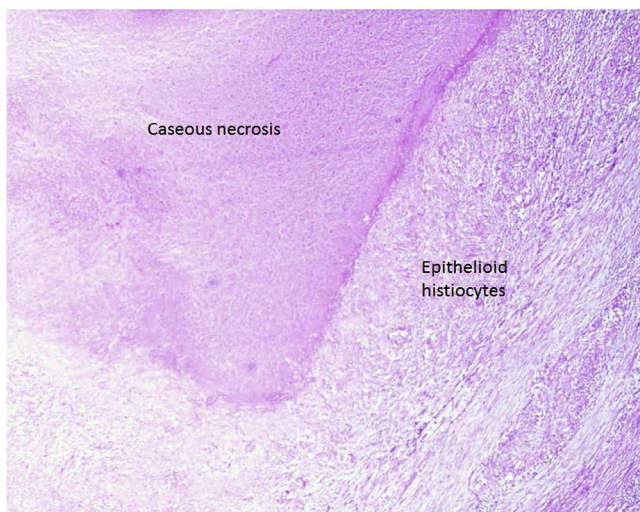


Fig. 7 – Hematoxylin and eosin stain. Caseous necrosis typically seen in granulomatous tuberculous (TB).



Fig. 8 – Ziehl-Neelsen stain. Acid fast bacillus (arrow).

maximize echoes from the rounded surface of microbubbles. A low mechanical index is required to prevent microbubble destruction. This can allow contrast visualization lasting up to a few minutes. A flash impulse of high mechanical index ultrasound can be used to destroy the visualized microbubbles, allowing for further boluses of contrast to be given if required. This technique, therefore, not only informs us as to the presence or absence of enhancement, but also provides dynamic assessment of blood flow and wash-out patterns.

No certain ultrasound feature is absolutely specific for characterizing a testicular lesion as either malignant or benign. However malignant lesions tend to show greater internal enhancement on both color Doppler and contrast enhanced ultrasound (CEUS) when compared with adjacent normal parenchyma as opposed to benign lesions, which tend to have reduced or absent enhancement.

The utility of contrast sonography appears to be in defining the presence or absence of internal vascularity in lesions with minima or slow flow. Malignant lesions on CEUS tend to demonstrate early enhancement compared with normal testicular parenchyma, which may persist but can wash out rapidly [21]. Complete absence of internal vascularity is a strong indicator of benignity and, therefore, CEUS can help in situations where color Doppler is unable to detect internal flow. Benign lesions will often show only peripheral enhancement, reflecting the paucity of internal vascularity. Although not diagnostic, malignant testicular lesions tend to demonstrate increased stiffness when compared with benign lesions and should be used in conjunction with other ultrasound parameters to improve specificity in characterizing a lesion as either benign or malignant [22,23].

The chronic, inflammatory granulomatous nature of tuberculosis results in central caseous necrosis and peripheral active inflammation, reflecting both histology and imaging [24]. Usually, the presence of epididymitis in addition to orchitis would strongly suggest an infective etiology as both phenomena are more often present together than in isolation as orchitis is often seen as a progression of epididymitis. Therefore, in the absence of epididymitis, further differentials for a testicular mass would need to be excluded including testicular malignancy, abscess, and torsion with or without infarction.

Testicular abscess is usually a consequence of epididymo-orchitis and would tend to present more acutely associated with erythema, swelling, pain, and severe tenderness. Intense peripheral color Doppler signal is often present with absent internal vascularity. Additionally, associated epididymal inflammation would almost always be present, signified by florid color Doppler signal, which is a distinguishing feature from testicular tumors, which will involve only the epididymis in locally advanced cases. If using elastography, an abscess would generally be of low stiffness in contrast to tumor.

Testicular torsion is an emergency, which often presents with a similar clinical picture to acute epididymo-orchitis, although the onset is often sudden, and inflammatory markers may not be raised. On ultrasound, the affected testis can show either increased or decreased blood flow, depending on whether there is complete or partial torsion and whether the testis has detorted. The affected testis is often heterogeneously hypoechoic and usually affects the entire testis rather than a focal geographic area.

Testicular tumors can vary in appearance according to the tumor type. Seminomatous tumors are classically well-defined homogeneous hypoechoic lesions, whereas non-seminomatous tumors are generally more irregular in outline and heterogeneous, sometimes containing calcification. Testicular lymphoma can be variable in appearance on grayscale ultrasound, but often exhibits florid internal vascularity. Regarding all types of testicular tumor, internal vascularity appears to be a common characteristic, which can help to differentiate from other pathologies on ultrasound. In addition to imaging, serum tumor markers such as alpha-fetoprotein, lactate dehydrogenase, and beta human chorionic gonadotropin can often be raised.

Another potential differential for a testicular mass is that of intratesticular hematoma, which could also appear as either a hyperechoic mass in the early stages or a hypoechoic mass in later stages with absence of internal flow and some peripheral reactive vascularity. Relevant clinical history of testicular trauma would help differentiate this from other causes of a testicular mass.

Clinicians should be aware of the systemic and localized complications of BCG therapy, including TB orchitis. Although more common causes such as tumor, infection, and torsion should be excluded, it is important to be aware of other causes such as this rare complication of BCG therapy in those treated for bladder cancer. Distinguishing between different types of testicular mass on ultrasound imaging can be challenging; however, the use of intravenous microbubble contrast agents and elastography can further contribute to understanding the dynamics and behavior of indeterminate testicular lesions. Consequently, this will increase specificity and sensitivity of diagnosis, helping to inform and direct patient follow-up and management.

REFERENCES

- [1] Fuge O, Vasdev N, Allchorne P, Green J. Immunotherapy for bladder cancer. *Res Rep Urol* 2015;7:65-79.
- [2] Morales A, Eiding D, Bruce AW. Intracavitary bacillus Calmette-Guérin in the treatment of superficial bladder tumors. *J Urol* 1976;116:180-3.
- [3] Gonzalez OY, Musher DM, Brar I, Ferguson S, Boktour MR, Septimus EJ, et al. Spectrum of bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. *Clin Infect Dis* 2003;36(2):140-8. doi:10.1086/344908.
- [4] Harada H, Seki M, Shinojima H, Miura M, Hirano T, Togashi M. Epididymo-orchitis caused by intra-vesical instilled BCG: genetically proven by using a multiplex polymerase chain reaction method. *Int J Urol* 2006;13(2):183-5.
- [5] Parker SG, Kommu SS. Post-intra-vesical BCG epididymo-orchitis: case report and a review of the literature. *Int J Surg Case Rep* 2013;4(9):768-70. doi:10.1016/j.ijscr.2013.05.017.
- [6] Demers V, Pelsser V. "BCGitis": a rare case of tuberculous epididymo-orchitis following intra-vesical Bacillus Calmette-Guérin therapy. *J Radiol Case Rep* 2012;6(11):16-21. doi:10.3941/jrcr.v6i11.1100.
- [7] Briceño-García EM, Gomez-Pardal A, Alvarez-Bustos G, Artero-Muñoz I, Mar Moliner M, Seara-Valero R, et al. Tuberculous orchiepididymitis after BCG therapy for bladder cancer. *J Ultrasound Med* 2007;26(7):977-9.
- [8] Salvador R, Vilana R, Bargallo X, Araque X, Nicolau C. Tuberculous epididymo-orchitis after intra-vesical BCG

- therapy for superficial bladder carcinoma: sonographic findings. *J Ultrasound Med* 2007;26(5):671–4.
- [9] Menke JJ, Heins JR. Epididymo-orchitis following intra-vesical bacillus Calmette-Guérin therapy. *Ann Pharmacother* 2000;34(4):479–82.
- [10] Asmussen L, Roosen JU, Hermann G. Granulomatous epididymo-orchitis, a rare complication of intra-vesical bacillus Calmette-Guérin therapy for urothelial cancer. *Scand J Urol Nephrol* 2009;43(4):331–3. doi:10.1080/00365590902930808.
- [11] Falkensammer C, Gozzi C, Hager M, Maier H, Bartsch G, Holtl R. Late occurrence of bilateral tuberculous-like epididymo-orchitis after intra-vesical bacille Calmette-Guérin therapy for superficial bladder carcinoma. *Urology* 2005;65(1):175.
- [12] Muttarak M, Lojanapiwat B, Chaiwun B, Wudhikarn S. Preoperative diagnosis of bilateral tuberculous epididymo-orchitis following intra-vesical Bacillus Calmette-Guerin therapy for superficial bladder carcinoma. *Australas Radiol* 2002;46(2):183–5.
- [13] Hansen CP, Mortensen S. Epididymo-orchitis and Reiter's disease. Two infrequent complications after intra-vesical bacillus Calmette-Guérin therapy. *Scand J Urol Nephrol* 1997;31(3):317–8.
- [14] Truelson T, Wishnow KI, Johnson DE. Epididymo-orchitis developing as a late manifestation of intra-vesical bacillus Calmette-Guerin therapy and masquerading as a primary testicular malignancy: a report of 2 cases. *J Urol* 1992;148(5):1534–5.
- [15] Michaelides M, Sotiriadis C, Konstantinou D, Pervana S, Tsitouridis I. Tuberculous orchitis US and MRI findings. Correlation with histopathological findings. *Hippokratia* 2010;14(4):297–9.
- [16] Bulbul MA, Hijaz A, Beaini M, Araj GF, Tawil A. Tuberculous epididymo-orchitis following intra-vesical BCG for superficial bladder cancer. *J Med Liban* 2002;50(1–2):67–9.
- [17] George VK, Russell GL, Harrison BDW, Green NA. Tuberculous epididymo-orchitis following intra-vesical BCG. *Br J Urol* 1990;66(1):101–2.
- [18] Colomba C, Di Carlo P, Guadagnino G, Siracusa L, Trizzin M, Gioe C, et al. A case of epididymo-orchitis after intravesical bacille Calmette-Guérin therapy for superficial bladder carcinoma in a patient with latent tuberculosis infection. *Infect Agent Cancer* 2016;11:25.
- [19] Sigrist RMS, Liau J, Kaffa AE, Chammas M, Willmann JK. Ultrasound elastography: review of techniques and clinical applications. *Theranostics* 2017;7(5):1303–29. doi:10.7150/thno.18650. eCollection 2017.
- [20] Gennisson JL, Deffieux T, Fink M, Tanter M. Ultrasound elastography: principles and techniques. *Diagn Interv Imaging* 2013;94(5):487–95. doi:10.1016/j.diii.2013.01.022.
- [21] Huang DY, Sidhu PS. Focal testicular lesions: colour Doppler ultrasound, contrast-enhanced ultrasound and tissue elastography as adjuvants to the diagnosis. *Br J Radiol* 2012;85(Spec Iss 1):S41–53. doi:10.1259/bjr/30029741.
- [22] Goddi A, Sacchi A, Magistretti G, Almolla J, Salvatore M. Real-time tissue elastography for testicular lesion assessment. *Eur Radiol* 2012;22(4):721–30. doi:10.1007/s00330-011-2312-2.
- [23] Auer T, De Zordo T, Dejaco C, Gruber L, Pichler R, Jaschke W, et al. Value of multiparametric US in the assessment of intratesticular lesions. *Radiographics* 2017;doi:10.1148/radiol.2017161373. Ahead of print.
- [24] Chirindel A, Martinez F, Gagliardi JA, Armm MF. Testicular tuberculosis without epididymitis simulating neoplasm. *Radiol Case Rep* 2015;3(3):133.