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REVIEW

New therapeutic approaches in the management of castration resistant prostate cancer

Ioannis K. Gkialas
Department of Urology, General Hospital of Athens, G.Gennimatas

Abstract

Building on decades of research, the past few years have yielded a near exponential increase in treatment modalities for patients with metastatic prostate cancer. Individually, these improvements in overall survival may appear modest, however, nearly all of them have a distinct mechanism of action and the possibility of synergistic effects have yet to be established. The promise of a durable impact on the mortality from metastatic prostate cancer will likely stem from further elucidation of molecular pathways involved in prostate cancer, as well as defining the optimal sequence of treatment for patients with metastatic prostate cancer.

Key words
prostate cancer; castration resistant; therapy

Adenocarcinoma of the prostate is the most common malignancy diagnosed in US men and the second leading cause of cancer related death with approximately 30,000 men succumbing to the disease in 2014[1,2]. Primary therapy for localized disease consists of either surgical resection or radiation therapy[3], however, for patients with recurrent or metastatic prostate cancer, treatment consists of androgen deprivation therapy through depletion or blockage of circulating androgens[4]. While initially effective, most men develop resistance as manifested by either clinical, radiographic or most commonly biochemical progression (increase in prostate - specific antigen despite "castrate" levels of testosterone)[5]. The development of castration resistant prostate cancer (CRPC) signals an inappropriate reactivation of the androgen receptor (AR) axis resulting in growth and proliferation[6]. Further, targeting of the AR pathway, through either the disruption of adrenal production of androgens with abiraterone acetate,[7,8] or inhibition of ligand binding using the second generation antiandrogen enzalutamide, results in increased survival for this population of men[9].

The greatest opportunity for curing prostate cancer occurs when a patient presents with early stage localized disease. Unfortunately, 10% - 20% of prostate cancer patients present with metastatic disease, and up to one - third of patients who present at an earlier stage will have disease recurrence despite surgical or radiotherapeutic treatment[10]. In over 80% of men with

Corresponding author:
Ioannis K. Gkialas, Department of Urology, General Hospital of Athens, G.Gennimatas E - mail: giangkialas@yahoo.gr

metastatic disease, primary androgen ablation leads to initial clinical improvement and reduction of serum PSA levels. However, almost all advanced metastatic cancers initially treated with androgen ablation will develop into castration resistant prostate cancer (CRPC), the major cause of morbidity and mortality death in these men. A significant number of medications have been recently approved for the treatment of CRPC[11]. From 2004 until 2010 only docetaxel was approved for "androgen independent (hormone refractory) metastatic prostate cancer", now referred to as metastatic CRPC (mCRPC). Historically, chemotherapy using docetaxel plus prednisone was the only therapy to demonstrate a survival advantage in advanced prostate cancer, making it the "gold standard therapy" in this disease state.

The first of these new drugs approved for mCRPC was an autologous immunotherapy, sipuleucel - T[12]. Since that 2010 approval, there have been other agents with differing modes of action that have demonstrated increased survival in the setting of mCRPC. These include the hormonal agents, abiraterone acetate and enzalutamide, the chemotherapeutic agent cabazitaxel, and bone targeting agents such as the radioactive radium 223 dichloride. The efficacy of androgen deprivation therapy (ADT) is routinely based on achieving castrate levels of serum T, arbitrarily defined as T ≤ 20 or 50 ng/dL. However, tissue androgen measurements in men with either locally recurrent or metastatic castration resistant prostate cancer (CRPC) clearly demonstrate that prostate and tumor androgen concentrations remain well within the range capable activating the androgen receptor (AR)[15, 16].

Abiraterone

Mechanism of action

CYP17A is a single enzyme that catalyzes the sequential hydroxylase (required for cortisol synthesis) and lyase (required for adrenal androgen synthesis) steps that are required for conversion of C21 pregnenolone and progesterone precursors to the C19 adrenal androgens, DHEA and AED. Abiraterone acetate, an orally administered, rationally designed small molecule derived from the structure of pregnenolone, irreversibly inhibits both the hydroxylase and lyase activity of CYP17A with approximately 10 - fold greater potency than ketoconazole. Because adrenal inhibition of CYP17A results in blockade of glucocorticoid as well as adrenal androgen synthesis, abiraterone is co - administered with prednisone to ameliorate the secondary rise in adrenocorticotropic hormone (ACTH) that can lead to excess mineralocorticoid synthesis[17].

A number of phase I and II studies initially demonstrated that abiraterone suppresses serum androgen levels and achieves prostate - specific antigen (PSA) and clinical responses in chemotherapy naïve and docetaxel - treated CRPC patients. Phase III studies in chemotherapy naïve (COU - AA - 302) and post - docetaxel treated men (COU - AA - 301) have confirmed these findings, resulting in FDA approval of abiraterone for men with metastatic CRPC either before or after treatment with chemotherapy.

In the post chemotherapy study (COU - AA - 301, 1195 men) the first interim analysis demonstrated a 3.9 month overall survival (OS) benefit for men receiving abiraterone, prompting the independent data monitoring committee (IDMC) to recommend the study be unblinded and men on the placebo arm be offered abiraterone[18]. All secondary endpoints were statistically significant in favor of abiraterone, including median time to PSA progression (8.5 months versus 6.6 months), median radiologic progression - free survival (rPFS, 5.6 months versus 3.6 months), and proportion of patients with > 50% PSA response (29.5% versus 5.5%)[19].

In the pre - chemotherapy study (COU - AA - 302, 1088 men), at a median follow up of 22.2 months abiraterone doubled rPFS from 8.3 months to16.5 months (HR 0.53, $p < 0.001$), accompanied by a trend for increased OS from 27.3 months in the placebo arm to not - reached in the abiraterone group (HR 0.75, $p = 0.01$ which did not meet the prespecified p value of 0.001), again prompting the IDMC to recommend the study be unblinded and men on the placebo arm be offered abiraterone[20]. All secondary endpoints were statistically significant in favor of abiraterone, including median time to opiate use (not - reached versus 23.7 months), time to initiation of chemotherapy (25.2 months versus 16.8 months), time to performance status decline (12.3 months versus 10.9 months), time to PSA progression (11.1 months versus 5.6 months), and proportion of patients with > 50% PSA response (62% versus 24%)[20].

Abiraterone is generally well tolerated, with 13% and 19% of abiraterone - treated patients in COU - AA - 301 and COU - AA - 302 (respectively) discontinuing therapy for adverse effects versus 18% and 23% of

placebo - treated patients. The most common adverse events in both groups were fatigue, back pain, nausea, constipation, bone pain and arthralgia, all in the range of 25% - 30%.

While clinical responses to abiraterone have been remarkable, not all patients respond and the majority ultimately progress with a rising PSA indicating reactivation of AR signaling[21]. Interestingly, recent case reports describe instances of an 'abiraterone withdrawal syndrome,' in which (generally transient) PSA declines occur following discontinuation of abiraterone, suggesting that mutations in the AR which can allow AR activation by exogenous corticosteroids may play a role[22,23]. Numerous studies evaluating the sequencing and combination of abiraterone with immunotherapy, chemotherapy and other AR targeted agents in multiple disease settings are underway.

Enzalutamide

Enzalutamide is an oral potent inhibitor of the androgen receptor (AR) signaling pathway, with actions including inhibition of ligand/receptor binding, nuclear translocation of activated androgen receptor, and inhibition of AR regulated nuclear transcription[24].

In an early trial, enzalutamide demonstrated antitumor effects irrespective of chemotherapy status[25]. In the subsequent phase 3 AFFIRM trial, enzalutamide significantly prolonged the survival of men with mCRPC after docetaxel chemotherapy and showed favorable results for all secondary endpoints[25]. More recently, enzalutamide significantly improved overall survival in men with chemotherapy - naïve mCRPC in the phase III, PREVAIL trial[25].

The international randomized phase III AFFIRM trial was conducted in 15 countries at 156 sites 11. A total of 1199 patients with progressive mCRPC were randomized in a 2:1 manner to enzalutamide 160 mg daily (n= 800) or placebo (n= 399). A planned interim analysis demonstrated a significant improvement in the primary endpoint of OS. Median OS was 18.4 months among patients receiving enzalutamide and 13.6 months among patients receiving placebo, an incremental benefit of 4.8 months. The hazard ratio for death was 0.63 ($p < 0.001$), indicating there was a 37% decrease in the risk of death compared with placebo. The superiority of enzalutamide over placebo was further shown for all secondary endpoints, including the time to PSA progression 8.3 versus 3.0 months; hazard ratio 0.25; $p < 0.001$; and rPFS 8.3 versus 2.9 months; hazard ratio 0.40; $p < 0.001$.

The PREVAIL study was a multinational, double - blind, randomized, placebo - controlled, phase 3 trial of enzalutamide. A total of 1,717 patients were enrolled in the study, with 872 in the enzalutamide group and 845 in the placebo group. Coprimary end points were radiographic progression - free survival and overall survival. Secondary end points included the time until the initiation of cytotoxic chemotherapy, the time until the first skeletal - related event, the best overall soft - tissue response, the time until PSA progression, and a decline in the PSA level of 50% or more from baseline[25].

In the PREVAIL study were involving men with metastatic prostate cancer who had not received previous chemotherapy, enzalutamide extended the time until radiographic progression or death, improved overall survival, and delayed the initiation of chemotherapy by a median of 17 months. The benefit of enzalutamide on radiographic progression - free survival was observed from the first assessment 2 months after randomization and conferred a relative reduction of 81% in the risk of progression or death.

Enzalutamide significantly reduced the risk of death by 29% over placebo, even though patients in the placebo group had received effective post - progression therapy more frequently and earlier than those in the enzalutamide group. The benefit of enzalutamide was observed as early as 4 months after randomization and was maintained throughout the study[25]. Overall, enzalutamide 160 mg orally daily was well tolerated by patients compared with the placebo control. Although the period of observation for the enzalutamide arm was more than twice that for the placebo group, the rates of AEs were similar in the two treatment arms. Overall there was a higher incidence of all grades of fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache in the enzalutamide arm compared with placebo. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo[26, 27].

Sipuleucel - T

Sipuleucel - T represents the first "personalized" immunotherapy for the treatment of cancer using a patient's own immune cells to overcome theself

- tolerance hurdle for the treatment of tumors. It is also important to stress that sipuleucel - T is not a gene therapy, since APCs are loaded with a purified recombinant protein and are not genetically manipulated or transfected with any form of viral or recombinant DNA or RNA. PAP was chosen as the target antigen for the prostate cancer treatment because it is expressed at detectable levels in more than 95% of prostate adenocarcinomas and is highly specific to prostate tissue[28, 29, 30].

Principles of cancer immunotherapy

Cancer is considered an immunosuppressive state that requires an intervention to boost adaptive immunity, including the antigen - specific defense mechanism. One of the key characteristics of cancer pathogenesis is the ability of the tumor cell to avoid immune destruction[31].

Active immunotherapy often referred to as "vaccine therapy" is designed to elicit a host immune response that specifically targets the tumor cell through a T - cell response cascade. Active immunotherapy requires the target antigen to be processed in a manner capable of inducing an immune response that generates anti - tumor activity. T - cells do not respond to soluble or naked protein antigens but rather require peptide fragments from the antigen to be "presented" to them on the surface of antigen - presenting cells (APCs) via human leukocyte antigen (HLA) molecules.

Prostate cancer as a target for immunotherapy

Training the host immune system to reject its own developing tumor has been a long unrealized dream. A variety of strategies were attempted in the past to stimulate an immune response in the prostate but none proved successful[32].

The prostate is a highly differentiated, gender - specific organ and prostate adenocarcinoma offers a variety of suitable antigen targets for cancer immunotherapy[33]. Many genes within the prostate are transcriptionally regulated by the androgen receptor and show highly regulated expression mostly restricted to the prostate gland or prostate cancer tissue. Included among such expressed genes are PSA, prostatic acid phosphatase (PAP), prostate - specific membrane antigen (PSMA), and prostate stem - cell antigen (PSCA).

Clinical evidence for immunotherapy with sipuleucel - T

Two early phase III randomized, double - blind, placebo - controlled trials with sipuleucel - T, (trials D9901 and D9902A) comparing sipuleucel - T to placebo in men with asymptomatic, mCRPC demonstrated significantly prolonged survival[34]. However, these smaller initial trials were combined for an initial FDA filing which led to the need to initiate a larger randomized, double - blind, placebo - controlled Phase III clinical registration trial known as the IMPACT study (Immunotherapy for Prostate AdenoCarcinoma Treatment) (D9902B). Briefly, in the 512 patient IMPACT study, the median OS was 25.8 months for men receiving sipuleucel - T and 21.7 months for patients who were treated with placebo (p= 0.03), a survival advantage of 4.1 months while possessing a relatively benign safety profile. Adverse events seen more often in sipuleucel - T treated patients than in those receiving placebo included predominantly chills, fatigue, and pyrexia that were Grade 1 or 2 in severity and of short duration (1 or 2 days), resulting in minimal discontinuation of treatment (< 2%).

The use of PSA in the setting of sipuleucel - T requires some clarification. PSA responses may not be observed in patients who have favorable overall survival benefit form sipuleucel - T. In an exploratory analysis of the IMPACT trial, the greatest magnitude of benefit with sipuleucel - T treatment was seen in patients with better baseline prognostic factors, and in particular those with lower baseline PSA values. This suggests that patients with less advanced disease may benefit the most from sipuleucel - T treatment.

Routine mCRPC follow up care is indicated after sipuleucel - T therapy. Patients and clinicians should be made aware that PSA may not be used as a definitive marker for response following immunotherapy. There is no consensus as to when patient should be reimaged, and that the median time to second treatment on the IMPACT study was 6 months driven primarily by imaging studies. Combining sipuleucel - T with other agents and further study of the optimum sequencing of immunotherapy will continue for the next few years[35].

Radium 223 dichloride

Prostate cancer frequently metastasizes to the bone primarily within the axial skeleton (vertebral bodies, pelvis, ribs, and skull) but may also occur in the long

bones[36]. Radiographically, osseous metastases are most often noted on 99 technetium methylene diphosphonate bone scintigraphy scans. However, newer modalities such as 18sodium fluoride PET and 18 fluorodeoxyglucose PET are more frequently being utilized given their increased sensitivity for detection. Clinically, bone metastases are the primary cause of morbidity and mortality for men with metastatic CRPC[37], with 80% - 90% of patients eventually developing metastatic disease[38]. Bone lesions may cause pain or skeletal related events such as spinal cord compression, fractures, or hypercalcemia.

The current radiopharmaceutical agents used against metastatic prostate cancer include strontium - 89, samarium - 153, rhenium - 186, and radium 223. Historically, primary outcomes included pain response, decrease in analgesic consumption, and quality - of - life. Radium 223 is the first radiopharmaceutical agent to demonstrate improved survival among patients with symptomatic bone - metastatic CRPC[39]. An α particle consist of two protons and two neutrons, a β particle is a high energy electron, while a γ ray is described as ionizing electromagnetic radiation. Each type of radiation has different advantages and disadvantages.

Alpha particles have the shortest range of these particle types, resulting in a dense deposition of energyclose to the origin of the particle emission. Alpha particles can be stopped by a sheet of paper, eliminating the need for any radiation shielding. Radium 223, as an alpha emitter, administered intravenously requires no radiation safety precautions such as particular sleeping arrangements, limited time or specified distance from children or pregnant women.

Radium 223 was recently approved by the FDA in 2013 for the management of men with metastatic castrate resistant prostate cancer after the publication of a randomized phase III trial which showed an overall survival benefit[39]. Radium 223, an alpha particle emitter, was originally selected given its half - life (11.4 days) that allowed convenient dosing, safe radon daughter isotope and high skeletal uptake in patients with osteoblastic metastases[40]. Pharmacokinetic studies demonstrated that within 24 hours < 1% of administered dose remained in circulation and was predominantly eliminated via the gastrointestinal tract. Pain relief was reported by 52%, 60%, and 56% of patients after either 1, 4, or 8 weeks respectively.

Radium 223 was recently approved by the FDA in 2013 for the management of men with metastatic castrate resistant prostate cancer after the publication of a randomized phase III trial which showed an overall survival benefit.

The phase III placebo controlled trial randomized 922 men with symptomatic bone - metastatic CRPC using a 2:1 ratio to receive six injections every 4 weeks of either radium 223 (50 kBq/kg) or placebo[39]. Entry criteria included at least two bone metastases without visceral metastases and either prior docetaxel treatment or inability to receive docetaxel. The primary endpoint was overall survival, with secondary endpoints of time to first SRE, time to alkaline phosphatase progression, alkaline - phosphatase response, alkaline - phosphatase normalization, time - to - PSA - progression, safety, and quality - of - life. Median survival was significantly increased from 11.2 months to 14.0 months with a hazard ratio of 0.695 in favor of radium 223. In addition, there was significant improvement in median time to SRE (13.6 months versus 8.4 months), time to alkaline phosphatase progression, and time to PSA progression (hazard ratio 0.671) favoring the treatment arm. Adverse events (AEs) were determined for any man who received > 1 injection in 762 patients. AEs were observed in 88% of the radium 223 patients and 94% of placebo - treated patients. Serious AEs were higher in the placebo group (43% versus 55%) and treatment discontinuation due to AEs was higher in the placebo group (13% versus 20%). Grade 3/4 hematologic toxicities were comparable between the two arms (neutropenia 3% versus 1%, thrombocytopenia 6% versus 2%, anemia 13% versus 13%). Given, that radium 223 is excreted via the intestinal system, which can manifest as diarrhea, nausea or vomiting, careful monitoring of the patient's oral intake and fluid status is crucial to prevent dehydration.

Radium 223 is the first radiopharmaceutical to provide a prolongation in overall survival in men with castration resistant prostate cancer. The safety profile of radium 223 is encouraging, in comparison to the β emitters, which may allow for increased dosing (phase I study planned), integration with myelosuppressive chemotherapy (NCT01106352, phase I/IIa study of safety and efficacy of radium 223 with docetaxel in patients with bone metastasis from castration resistant prostate cancer), or novel AR targeting agents (phase I study planned with enzalutamide and abiraterone acetate).

Conclusion

With the rapid introduction of multiple new agents, the lack of clarity regarding the optimal integration of these drugs into the management paradigm of patients with advanced prostate cancer is unsurprising. Other drugs such as cabozantonib, ipilimumab and custirsen are in late stage evaluation and may in the near term add to the armamentarium and quandary of managing patients with advanced prostate cancer[41].

Περίληψη

Η ανάπτυξη των νέων προσεγγίσεων στη διαχείριση του προχωρημένου μεταστατικού καρκίνου του προστάτη έχει σημειώσει μεγάλη πρόοδο τα τελευταία χρόνια.Οι βασικές θεραπείες στέρησης ανδρογόνων (ADT) έχουν τελειοποιηθεί και πολλοί νέοι παράγοντες έχουν εγκριθεί από το 2010 για τη θεραπεία τόσο του μεταστατικού όσο και του ευνουχοάντοχου καρκίνου του προστάτη (mCRPC). Η κατανόηση της θεωρίας αυτών των νέων παραγόντων και η εστιασμένη προσεγγισή τους σε πρακτικές κλινικές εφαρμογές είναι απαραίτητες για τη βελτίωση των θεραπευτικών αποτελεσμάτων. Καθώς η αντιμετώπιση αυτών των ασθενών με προχωρημένη νόσο γίνεται πλέον πολυδιάστατη και η χρήση αυτών των παραγόντων επεκτείνεται, σε ουρολόγους, ογκολόγους και ακτινοθεραπευτές θα πρέπει ολοι να γίνουν πιο εξοικειωμένοι με τις νέες θεραπευτικές επιλογές.

Λέξεις ευρετηριασμού

προστατικός καρκίνος, ευνουχοάντοχος, θεραπεία

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REVIEW

Testicular microlithiasis: Clinical significance and review of the literature

Dimitrios M. Baltogiannis[1], Athina C. Tsili[2]
[1]Department of Urology, Medical School, University of Ioannina
[2]Department of Clinical Radiology, Medical School, University of Ioannina

Abstract

Testicular microlithiasis (TM) is an uncommon and asymptomatic benign entity, typically detected incidentally on scrotum sonography. Typical sonography findings include the emergence of tiny, highly reflective foci within the testis, which are not accompanied by acoustic shadowing. Five (5) or more foci with the above features, present in at least one US image, is the most commonly used criterion for the diagnosis of classic TM. TM has been associated with diverse pathologies, including testicular carcinomas, intratubular germ cell neoplasia, infertility, cryptorchidism, atrophy and testicular dysgenesis. To date, there is no documented evidence that TM is a predisposing factor for testicular neoplasia. Therefore, no surveillance is warranted for men found to have TM alone in the ultrasound examination. However, for men with predisposing or risk factors for a testicular germ cell neoplasm, such as a previously diagnosed testicular carcinoma, a family history of the disease, cryptorchidism, infertility, testicular atrophy and gonadal dysgenesis, surveillance is mandatory.

Introduction

Testicular microlithiasis (TM) is an uncommon, asymptomatic condition, in which small calcifications are observed inside the testicular parenchyma[1-6]. This is usually an incidental finding in the sonography of the scrotum[1-6]. The incidence of testicular microlithiasis in the general population is not accurately known. The reported rates of testicular microlithiasis range from 2.4% to 5.6% in asymptomatic adults, and from 0.6 to 9% in symptomatic men[1, 4, 7-18]. In childhood, the reported incidence of the condition in the asymptomatic population is 4.2%, and 2% in boys with clinical symptomatology [4, 7, 18-22].

Key words
Testicular microlithiasis; testicular germ cell neoplasm; sonographic control

Pathogenesis - histological findings

The pathogenesis of testicular microlithiasis appears to be related to the disruption of the basement membrane of the seminiferous tubules and the deposition of glycoprotein rings in their lumen, which is then calcified. In electron microscopy, the size of the microcalcifications does not exceed 1 mm; these consist of a central calcified ring, surrounded by concentric layers of collagen fibres [1, 2, 4, 8-10]. According to another theory, the microcalcifications are located within the testicular stroma, already since the earliest stages of embryogenesis of the gonads.

The aetiology of testicular microlithiasis remains

Corresponding author:
Dimitrios Baltogiannis, Assistant Professor of Urology, Medical School, University of Ioannina
Street: 14 Alketa Street, 45221 Ioannina, Tel. 6977692974, E - mail: dbaltog@cc.uoi.gr

unclear. Although metabolic and inflammatory causes have been proposed, as have as differences in the incidence of microlithiasis depending on ethnicity and geographical area, it appears that the condition is more related to a dysfunction of the Sertoli cells, which are responsible for phagocytosis and the elimination of cellular debris from the seminiferous tubules [8].

Sonography findings

The sonography findings of testicular microlithiasis were initially reported in 1987 by Doherty et al. and were detailed in 1994 by Janzen and Backus, who first described the sonographic criteria of classic TM[1, 11]. These consist in the emergence of multiple tiny highly reflective foci, which are usually located in both testes, with diameters ranging from 1 to 3 mm **(Figure 1)**. Due to their very small size, these foci are not accompanied by acoustic shadowing. The criterion that has been used for the diagnosis of classic TM comprises the emergence of five (5) or more foci with the above features, present in at least one US image[1, 4, 11, 23 - 26]. The term limited microlithiasis (limited TM) covers the detection of at least one stone in the testicular parenchyma, but their total number is no more than five. In literature, terms such as starry sky or snow - storm pattern have been used to describe the sonographic findings of TM[24]. The number and distribution of the stones varies considerably. The typical pattern is that of a diffuse, bilateral, symmetrical testicular insult, but the localisation of microlithiasis may be distal, segmental, unilateral or asymmetric. The extent of testicular insult has been classified in grades. We should mention the classification of classic TM as grade I: 5 - 10 stones **(Figure 2)**, II: 11 - 20 stones, III: 21 - 30 and IV: more than 30 stones per US image **(Figure 1)**[25]. However, it should be stressed that the sonographic findings are not always associated with the pathological findings.

The relationship of TM with other benign entities

Although TM is an asymptomatic and often incidental finding in ultrasound testing, it has been reported to co - exist with a multitude of benign conditions, including torsion of the testis or parts thereof, testicular infarction, varicoceles, testicular atrophy, epididymal cysts, epidermoid cysts **(Figure 1)**, Klinefelter syndrome and hypogonadism[2 - 4, 9, 10, 11, 23].

A strong correlation has been reported between

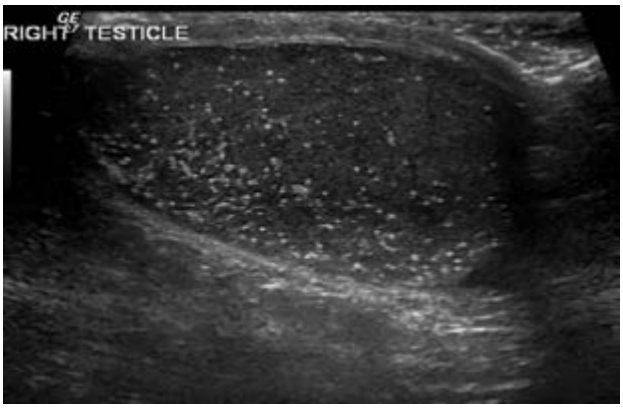

Figure 1. *Classic grade IV microlithiasis of the right testis, in a 20 - year old man. Scrotal ultrasound; the longitudinal section highlights the presence of numerous, small, highly reflective foci, within the parenchyma of the right testis. These foci are not accompanied by acoustic shadowing. The patient underwent radical left orchiectomy 18 months ago. The histological report indicated an epidermoid cyst of the testis*

testicular microlithiasis and infertility. According to literature, its frequency in the subfertile population ranges from 0.8 - 20%[10, 14, 27, 28].Testicular microlithiasis is also associated with cryptorchidism **(Figure 2)** or delayed testicular descent[2, 10, 18, 23, 29]. In a study of 30 patients, the presence of microliths in the testicular parenchyma was linked to cryptorchidism at a rate of 6.7%[10]. TM has also been linked to male pseudohermaphroditism, Down syndrome, McCune - Albright syndrome, Frasier syndrome, fragile X chromosome syndrome in siblings and pseudoxanthoma elasticum[2-4,10,11,23,30,31].The presence of microlithiasis in patients with pulmonary alveolar microlithiasis, empty sella syndrome, neurofibromatosis and AIDS has also been reported.

The relationship of TM with testicular neoplasms - the view of the past

For several years, it was perceived that testicular microlithiasis was a primary manifestation of a disorder of the testicular parenchyma and that this disorder resulted in an increased incidence of malignant testicular germ cell neoplasms (GCNs) [1.4, 8, 10, 21, 28, 32 - 36]. The reported frequency of coexistence of testicular neoplasms in subjects with microlithiasis is 30 - 35%, or 6 - 46% in adults and up to 12.5% in children **(Figure 3)**.[21] The risk of developing a malignant testicular neoplasm was stated to be 2 to 20 times higher than in the healthy population [1].

In a retrospective study of 1,535 soldiers with varied

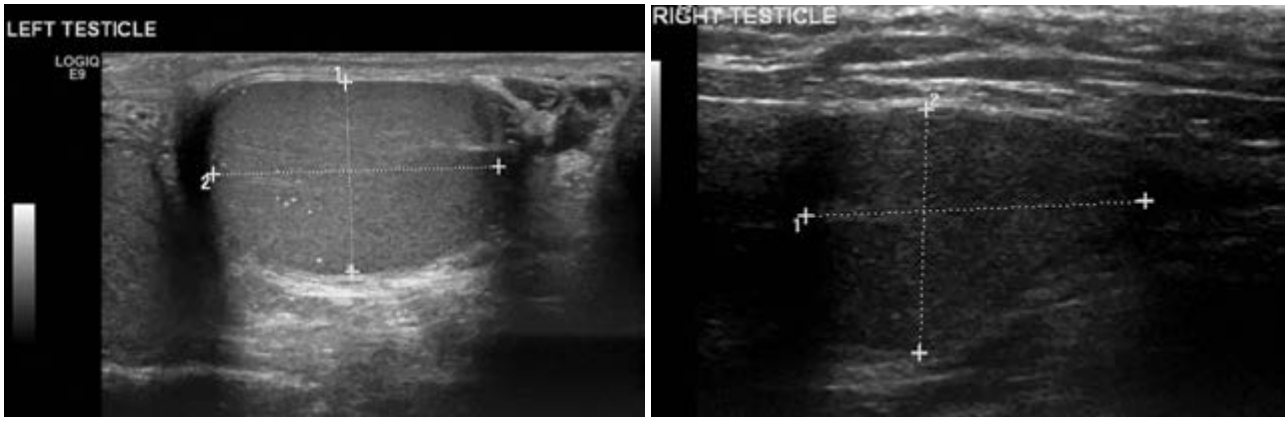

Figure 2. *Classic grade I microlithiasis of the left testis, in a 20 - year old man with a history of right cryptorchidism. Scrotal ultrasound; (a) the longitudinal section of the left testis reveals the presence of five microliths within its parenchyma. (b) the longitudinal section of the right testis shows this to be smaller and with hypoechoic imaging compared to the contralateral testis.*

scrotal symptomatology, the reported frequency of microlithiasis was 4.1%, with a mean age of 35.4 years at diagnosis. In the same report, 46% of subjects with microlithiasis also suffered from a primary testicular carcinoma[33].

Factors that are considered of increased risk for developing malignant testicular germ cell neoplasms, such as subfertility and cryptorchidism, are closely correlated with microlithiasis[7, 14, 27 - 29, 32]. This condition has also been associated with testicular intratubular germ cell neoplasia (ITGCN), which is considered a pre - malignant condition[4, 7, 32 - 34, 37, 38]. Nearly all malignant testicular germ cell neoplasms are believed to originate from a common cell, the carcinoma in situ (CIS) cell, except for the uncommon spermatocytic seminomas found in adults and neonatal testicular neoplasms (yolk sac tumours and mature teratomas)[37]. The development of invasive testicular GCNs is expected to be observed in 50% of people with ITGCN over 5 years, if left untreated, and in 70% of cases after 7 years[37]. It is estimated that all patients with ITGCN will eventually develop invasive testicular neoplasms, although some extremely rare cases of burned out CIS have been described[37].

There are studies reporting an increased incidence of ITGCN in subfertile men with sonographic findings of microlithiasis.[7] It has also been reported that individuals with microlithiasis and atrophic testes are more likely to develop ITGCN.[7] In a study of 263 subfertile men, 53 (20%) had microlithiasis findings[3, 39]. Six of 30 patients in the same report, with bilateral localisation of microlithiasis, were diagnosed with ITGCN, leading to the conclusion of a significantly higher incidence of ITGCN in the subfertile

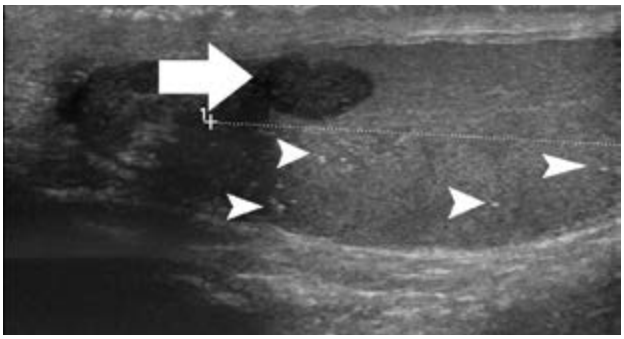

Figure 3. *Seminoma of the left testis and findings of classic grade I microlithiasis in a 32 - year old man. Scrotal ultrasound; longitudinal section of the left testis and ipsilateral epididymis. The neoplasm emerges as a mainly homogeneous hypoechoic lesion (arrow) in the upper pole of the testis. Coexisting findings of classic grade I microlithiasis (arrowhead)*

population with bilateral microlithiasis compared to those with a unilateral localisation[39].

After monitoring subfertile men for 24 months, Negri et al. report a 24.3% chance of development of GCNs in men with microlithiasis[32].In contrast, Kosan et al. report that none of the 194 subfertile men in their study, which included 18 men with microlithiasis findings, developed testicular GCNs after being monitored over 19.5 months [32]. Husmann et al. report that ultrasound testing in a 2 - year follow - up after preceding orchidopexy in men with cryptorchidism showed microlithiasis in the resected testes in 10% of cases[29]. The monitoring of 19 individuals in the same study for 8 years showed the delayed development of testicular malignancies in 2 cases. This report concluded that the risk of malignancy in men with cryptorchidism is 2 - 3 times greater in the presence of microlithiasis,

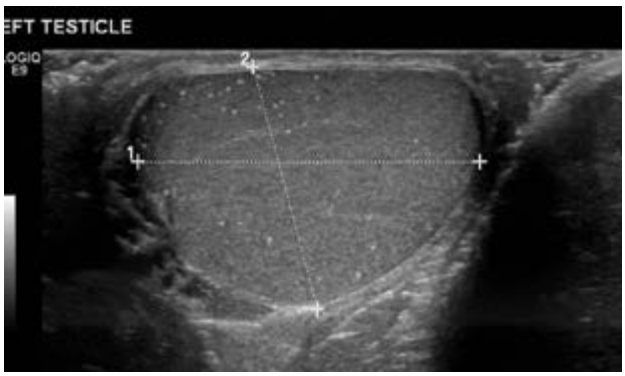

Figure 4. *Microlithiasis of the left testis in a 31 - year old man with a history of right orchiectomy due to a seminoma. Scrotal ultrasound, longitudinal section*

compared to men without this sonography finding[29].

TM has also been associated with the development of malignant neoplasms in the contralateral testis in patients with a history of orchiectomy due to GCNs[4]. Bach et al. reported the development of contralateral malignant testicular neoplasms in 22% of men with microlithiasis, compared to 2% of patients without microlithiasis[4,40]. In patients with a history of surgery for testicular GCNs, an increased incidence of ITGCN in the contralateral testis is also reported, when microliths coexist in this, which, if not treated will lead to development of a delayed neoplasm (the relative risk is about 28.6%)[12]. Other studies report the existence of microlithiasis in the contralateral testis in 20% of people with primary germ cell neoplasms **(Figure 4)**[32].The risk of coexistence of ITGCN in the same patient group is 8.9 times higher for men with microlithiasis, compared to patients with a similar history of malignancy, but without microlithiasis[32].

The reported incidence of testicular microlithiasis is also higher in the relatives of patients with GCNs, leading to the conclusion that it is a familial predisposing factor for the development of testicular neoplasms. Epidemiological studies have shown that the likelihood of development of malignancies is 8 - 10 times greater for the brothers and 4 times greater for the fathers and male children of men with testicular germ cells neoplasms[18, 41, 42].

The association of testicular microlithiasis with malignancy is further supported by literature reports of some isolated cases of patients with sonographic diagnosis of microlithiasis, whose monitoring showed delayed development of testicular germ cell neoplasms [3, 5, 10, 13, 15, 43 - 47]. The mean time for neoplasm development in these patients was 48 months from initial diagnosis of microlithiasis, and the findings concerned extended microlithiasis in some cases and the presence of few microliths in others.

Finally, in rare cases, testicular microlithiasis has been associated with extragonadal germ cell tumours, localised in the mediastinum and/or abdomen, usually in adults[4, 21, 37]. A similar correlation has been reported in childhood, coupled with Klinefelter syndrome[4, 21, 37].

Based on the above data, testicular microlithiasis was considered a pre - malignant condition and the surveillance of these men had been proposed, aiming to the early diagnosis of testicular neoplasms. The protocols proposed in literature displayed significant differences, ranging from simple monitoring, accompanied by self - examination or not, to the measurement of tumour markers in blood serum, to recommendations for testicular biopsy in combination with regular visits to the urological clinic and sonography[10 - 12, 15, 32, 33, 48]. Another monitoring protocol recommended an annual scrotal sonography in men with microlithiasis aged 20 - 50 years. Some authors have proposed control with axial tomography of the chest and abdomen at diagnosis of microlithiasis, followed by periodic sonographies at intervals of 6 - 12 months. In 2006, studying the protocols for monitoring men with TM in England, Ravichandran et al. reported significant variations, concluding that most urologists are not entirely convinced as to the usefulness of screening[48]. However, a significant proportion continues to monitor these men for a long time, which is also different: some continue monitoring for life, others until the age of 55 years and some stop if the sonographic findings remain stable after 5 years. The screening protocols included sonographies combined with clinical examinations, usually every year or every six months or at greater intervals[48]. However, it should be emphasised that the above monitoring protocols will create a huge economic burden on the National Health System in the future. It is also known that an interval of 3 - 6 months intervenes from the moment a man feels a testicular mass on palpation to the time he seeks medical assistance; this delay does not have a significant impact on prognosis and on the treatment of testicular neoplasm. Given the satisfactory response to treatment of the majority (90%) of malignant testicular

neoplasms, it is doubtful whether the earlier diagnosis of the neoplasm by sonography in fact contributes to a better final outcome, compared to diagnosis by clinical examination[48].

The relationship of TM with testicular neoplasms - the current view

According to the latest literature, there seems to be no documented proof that TM is a predisposing factor or cause of the development of testicular neoplasms. The prevailing view now is that microlithiasis is rather a manifestation of a disorder of the testicular parenchyma, and not a poorly defined condition that predisposes both for the development of malignancies and for coexistence with benign conditions[1,4,5,12,14,15,30]. A review of recent literature shows that TM is not associated with an increased risk of developing GCNs in asymptomatic men. Recent studies report smaller percentages of coexistence of malignant testicular neoplasms and microlithiasis and the non - delayed development of malignancies after the long - term monitoring of these men[1,4,5,12,14,15,30,32].

A study of 2,656 men who came for sonography testing by Richenberg et al. reported 51 (1.92%) cases with TM, of which none developed neoplasms following monitoring for a mean of 33.3 months[25]. Following a review of the literature, the same author team reports the development of malignancies in 4 out of 389 men. Excluding three incidents with predisposing factors for developing testicular neoplasia, only one case of 389 developed a malignancy during the follow - up, leading to a probability of about 1 in 100 for the delayed development of testicular GCNs in otherwise healthy people with microlithiasis[25].

The presence of malignant testicular GCNs has rarely been reported in healthy, asymptomatic men[32]. Serter et al. report that microlithiasis rates are 2.4% in asymptomatic men without presence of malignant neoplasms[32]. A study of 1,504 asymptomatic men aged 18 - 35 years who visited a military hospital reported the presence of microlithiasis in 84 men (5.6%) and in one case the presence of a testicular GCN, without coexistence of microlithiasis however[11]. The same study reports a greater frequency of microlithiasis in black men (14.1%) compared to white (4%), which raises questions about the relationship of microlithiasis with neoplasias, as the incidence of testicular malignancies is significantly lower in the black race (0.9/100,000) than the white race (5/100,000).[11]

After 1987, literature reports 15 cases of men with testicular microlithiasis and delayed development of malignant neoplasms after a mean period of 35.7 months[5, 17].The majority of these cases however are retrospective reports or isolated incidents and the correlation of microlithiasis with testicular cancer is not well documented or concerns high - risk individuals[5, 17].

According to the above data, not all persons with TM will develop malignant neoplasms. Nonetheless, microlithiasis is a worrying finding in men with predisposing factors for testicular neoplasms. In this population, the existence of microlithiasis is associated with an 8.5 - fold and 10.5 - fold higher risk, respectively, for the diagnosis of concurrent malignant testicular germ cell neoplasms and ITGCN compared to the general population[14, 32].The delayed appearance of testicular malignancies has also been reported in these cases[14, 32].

The high - risk group includes men with a history of testicular GCNs (the relative risk is 25 times higher than in the healthy population), a history of cryptorchidism (relative risk: 4.8), family history of testicular malignancies (relative risk: 3 - 10), subfertility, testicular atrophy and gonadal dysgenesis[12, 15, 16, 42, 47].

Patients with Down's syndrome are also at high risk[30]. The reported incidence of microlithiasis in these cases is significantly higher than in the rest of the population. Other population groups that belong to the high - risk category are patients with extragonadal germ cell tumours, as well as children with syndromes associated with a mutation of the WT1 gene, McCune - Albright syndrome and Klinefelter syndrome[22, 27].

Conclusions

The above show that people with TM without predisposing factors for the development of malignant neoplasms not require monitoring, but only self - examination of the testes. Monitoring, mainly by regular clinical examinations and sonography, is only necessary for men with microlithiasis and predisposing factors for developing testicular germ cell neoplasms. In these individuals, the emergence or suspicious findings at sonography or at the clinical examination should lead to a testicular biopsy or orchiectomy. The above are included in the recent guidelines of the European Association of Urology[49, 50].

Περίληψη

Η μικρολιθίαση του όρχεως αποτελεί μια σπάνια, ασυμπτωματική καλοήθη οντότητα, κατά κανόνα τυχαίο εύρημα κατά τον υπερηχοτομογραφικό έλεγχο του οσχέου. Τα τυπικά υπερηχοτομογραφικά ευρήματα περιλαμβάνουν την ανάδειξη πολύ μικρού μεγέθους, έντονα υπερηχοικών εστιών εντός του όρχεως, οι οποίες δεν συνοδεύονται από ακουστική σκιά. Σαν κριτήριο για την διάγνωση της «κλασσικής μικρολιθίασης» θεωρείται η ανάδειξη πέντε (5) ή περισσοτέρων εστιών, με τους ανωτέρω χαρακτήρες σε ένα τουλάχιστον οπτικό πεδίο κατά τον υπερηχογραφικό έλεγχο. Η μικρολιθίαση του όρχεως έχει συσχετισθεί με ένα μεγάλο αριθμό παθολογικών καταστάσεων, μεταξύ αυτών το καρκίνωμα του όρχεως, η ενδοσωληναριακή νεοπλασία από γεννητικά κύτταρα, η υπογονιμότητα, η κρυψορχία, η ατροφία και η δυσγενεσία του όρχεως. Μέχρι σήμερα, δεν υπάρχει τεκμηριωμένη απόδειξη ότι η μικρολιθίαση του όρχεως αποτελεί προδιαθεσικό παράγοντα για την ανάπτυξη καρκινώματος του όρχεως. Για αυτό το λόγο δεν συστήνεται παρακολούθηση των ανδρών με μοναδικό εύρημα την μικρολιθίαση κατά τον υπερηχογραφικό έλεγχο. Αντίθετα, σε άνδρες με προδιαθεσικούς η παράγοντες για καρκίνωμα του όρχεως από γεννητικά κύτταρα, όπως παλαιό ιστορικό κακοήθειας του όρχεως, οικογενειακό ιστορικό της νόσου, κρυψορχία, υπογονιμότητα, ατροφία ή δυσγενεσία των γονάδων η παρακολούθηση είναι αναγκαία.

Λέξεις ευρετηριασμού

Μικρολιθίαση όρχεως, κακόηθες νεόπλασμα όρχεως από γεννητικά κύτταρα, υπερηχοτομογραφικός έλεγχος

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ORIGINAL PAPER

Intrascrotal adenomatoid tumour: A report of seven cases and review of the literature

Tomasz Golabek[1], Jakub Bukowczan[2], Tomasz Wiatr[1], Mikolaj Przydacz[1], Lukasz Belch[1], Piotr Chlosta[1]
[1] Department of Urology, Collegium Medicum of the Jagiellonian University, Krakow, Poland
[2] Department of Endocrinology and Diabetes Mellitus, Diabetes Resource Centre, North Tyneside General Hospital, North Shields, United Kingdom

Abstract

Adenomatoid tumours (ATs) are rare intra - scrotal neoplasms. Although a diagnosis of this type may be suspected when found in the epididymis, an intra - testicular location can cause a diagnostic and therapeutic dilemma. Thus, we report our experience with intra - scrotal adenomatoid tumours - 5 epididymal, 1 intra - testicular, and 1 involving the epididymis and testis, as well as a literature review to better understand this benign but clinically significant lesion.

Key words
adenomatoid tumour; benign epididymal tumour; intra - scrotal neoplasm

Introduction

Adenomatoid tumours (AT) may be found in both male and female genital tracts, but are generally considered uncommon findings. In men, they usually arise in the epididymis but may also involve the testicular tunica and spermatic cord[1,2]. In women, these benign neoplasms have been located in the uterus, fallopian tubes, and rarely in the ovary[3]. The origin of adenomatoid tumours has been a controversy for many years, however, comparative electron microscopic and immunohistological studies have demonstrated a mesothelial origin[3,4]. In most cases of adenomatoid tumour involving the epididymis, the diagnosis may be strongly suspected as this type of neoplasm represents the most common lesion in that particular location[3,5]. Additionally, an asymptomatic course and an incidental finding of a small slow growing and painless mass adjacent to the testis, are both in favour of such diagnosis. Nevertheless, in some cases, especially when it originates from within the tunica albuginea with secondary involvement of the adjacent testicular parenchyma, AT may be indistinguishable from a malignancy and may give rise to a clinical quandary. In this article, we present a retrospective analysis of seven cases of adenomatoid intrascrotal tumours, and we also include a brief literature review.

Material and methods

All male patients who underwent surgery for a scrotal mass between August 1984 and July 2014 were identified using the hospital patient registration

Corresponding author:
Tomasz Golabek, Department of Urology, Collegium Medicum of the Jagiellonian University, ul. Grzegorzecka 18,31 - 531 Krakow, Poland, Tel.: +48 (12) 424 79 50 , Fax: +48 (12) 424 79 70, E - mail: elementare@op.pl

database and histology registry database. Patients with histologically - proven adenomatoid intrascrotal tumours were included for analysis. A retrospective review of the charts confirmed the diagnosis.

The following data were collected and selected for analysis: age, presenting complaints, location of the lesion, initial and final diagnosis, type of procedure, and complications.

Results

The clinical data of all men with benign adenomatoid tumours are shown in **Table 1**.

An incidence of 1.6 per 100,000 hospital admissions was found. There were 7 intrascrotal ATs diagnosed between 1984 and 2014. Of these, one was located within the testis, five within the epididymis and one within the testis and epididymis.

Adenomatoid tumours comprised 26.3% of all epididymal neoplasms and they represented 0.85% of all testicular tumours. All patients were of Caucasian origin. Their age ranged from 34 to 69 years (mean 45 years). Two patients were symptomatic and complained of intermittent scrotal pain which resolved following the surgery. Four tumours were found incidentally by the patients themselves after self - examination and one was discovered at hydrocelectomy. The time from the discovery of a scrotal mass by a patient to seeking a medical attention ranged from 4 months to 2 years and it was shorter in two patients who had a history of previous blunt scrotal injury. There was no familial incidence of intrascrotal tumours recorded, and all patients, except one who had a 2 - year history of hypertension, had no other medical conditions.

On physical examination, a non - tender mass was noted in all cases. It was confined to the tail of the epididymis in four patients, to the head of the epididymis and upper pole of testis in one patient, and to the lower pole of the testis in one another. A hydrocele was diagnosed in one case.

Three patients had local excision of the tumour, one had a partial epididymectomy, one had a total epididymectomy, and one had a simple orchidectomy. The youngest patient who had a short history of a testicular mass underwent radical orchidectomy. No recurrence was found during the follow - up ranging from one to three years.

Discussion

Adenomatoid tumour of the male genital tract has been recognised since 1945[6]. It comprises 32% of all paratesticular tissue neoplasms and it is the most common benign epithelial tumour of the epididymis representing up to 77% of all cases[5,7]. ATs may be found in the tunica albuginea of the testis in approximately 14% of cases and, rarely, in the spermatic cord, prostate, ejaculatory ducts and scrotal capes[3].

The reported incidence 1 - 2 per 100,000 admissions[8], which is similar to our findings, seems to be an underestimation, considering its frequent asymptomatic course. Moreover, the misdiagnosis of a spermatocele could clearly affect its true prevalence.

Although the tumour may be found anywhere worldwide, there are significant geographic variations in the reported incidence rates with Caucasian men being the most commonly affected group (9:1)[9]. Adenomatoid tumours can occur across all ages, however, they remain most commonly diagnosed in the third and fourth decades of life[1,2]. There is no predilection to a particular side[9], confounding reports regarding the predominant location within the epididymis exist, however [3,10,11]. In our series, the tail of the epididymis was involved in three cases, while the head of the epididymis was involved in two patients.

An intra - testicular location of AT occurs only exceptionally with no more than eleven cases involving the testicular parenchyma having been reported so far [2,12,15]. In our series, only one out of seven men had a tumour located within the testicular parenchyma.

Clinically, adenomatoid tumour presents as a slow growing, small, solid, well - demarcated mass, without a capsule nodule and which does not transilluminate [1 - 3]. In older men it is usually asymptomatic and found on routine examination or at time of surgery. On the other hand, in younger patients, a more rapidly progressing mass which is often associated with pain seems to be a common manifestation[8,13]. A similar pattern of presentation was found in our series. The observed differences could likely be explained by more frequent self - examination and a greater awareness among rather young males but also by possibly different natural history.

Approximately 20% of ATs are associated with the hydrocele. In these cases, this benign neoplasm is found

TABLE 1 *Physical, clinical and radiological characteristics of the patients with benign adenomatoid tumours*

Case	Age (yrs)	Presenting symptoms	Clinical findings	Other studies	Procedure	Histology
1	34	Incidental finding, 1 year	Small, hard, non - tender mass of the head of the right epididymis	Frozen sections: no evidence of malignancy	Partial epididymectomy	Adenomatoid tumour of the epididymis
2	37	Incidental finding, 2 years	Small, hard, non - tender mass in the inferior pole of the left testis	BHCG, AFP,LDH: normal; Frozen sections: no evidence of malignancy	Local excision	Adenomatoid tumour of the testis involving tunica albuginea
3	48	Intermittently painful small scrotal mass, 5 months; prior scrotal injury	Small, hard, non - tender mass of the left epididymal tail	No tests performed	Local excision	Adenomatoid of the epididymis
4	69	Intermittently painful, large scrotal mass, 1 year	Large 9x6x5 cm, non - tender, right hydrocele; Hydrocele and 6 cm mass attached to the right epididymis found at surgery	No tests performed	Scrotal orchidectomy	Right hydrocele and adenomatoid tumour of the right epididymis
5	40	Incidental finding, 6 months, prior scrotal injury	Small, hard, non - tender mass of the right epididymal tail	US: calcified haematoma in the right epididymis	Epididymectomy	Adenomatoid of the epididymis
6	49	Incidental finding, asymptomatic, 2 years, increase in size over 1 year	Small, hard, non - tender mass of the right epididymal tail	US:3x1 cm hypo - echoic tumour	Local excision	Adenomatoid of the epididymis

Key: yrs= years; BHCG= Human Chorionic Gonadotropin; AFP= Alfa Fetoprotein; LDH= Lactate dehydrogenase; US= scrotal ultrasound

incidentally following hydrocelectomy[7]. Trauma of the scrotum preceding discovery of the tumour has been reported in few patients, giving rise to a controversy associated with its histogenesis[8]. Still, comparative electron microscopic and immunohistological studies have demonstrated similarities with the mesothelium [3,4], therefore the association with trauma seems rather anecdotal. Nonetheless, two of our patients had blunt scrotal injury 3 to 5 months before the discovery of a lesion. Five percent of men present with symptoms suggesting acute epididymitis[14].

Scrotal ultrasonography is a recommended preoperative imaging modality as it determines the location and differentiates cystic from solid lesions. However, in cases of intratesticular ATs, its usefulness is limited since they may appear as hypo - , iso - , or hyperechoic lesions[13,14]. Likewise, the Nuclear Magnetic Resonance imaging may not provide the definitive diagnosis[15].

Adenomatoid tumours have no malignant potential, and no cases of metastasis or recurrence after excision have been reported. Treatment, therefore, is by surgical excision[1,16]. If a benign lesion of the testis is suspected, a fine needle aspiration cytology or an intra - operative biopsy should be performed prior to dividing the spermatic cord. This approach allows to avoid unnecessary orchidectomy. Cytological features of AT include smears containing sheets of epithelial cells and clusters of monomorphic cells with round or oval nuclei and inconspicuous nucleoli[17,18]. Cytoplasm is clear and vacuolated in the Papanicolaou stain and stains pink with the Giemsa stain. Naked nuclei and

fragments of stroma along with few lymphocytes can also be seen[18].

Postoperative histological examination provides the final diagnosis. Microscopically, adenomatoid tumours are characterized by three basic patterns: tubules, cords, and small nests lined by, or formed of, cells that are cuboidal with moderate to abundant basophilic, eosinophilic, or vacuolated cytoplasm. The stroma contains fibroblasts, blood vessels and smooth muscle and is usually fibrous and occasionally hyalinized [1,3,17]. In view of the range of microscopic appearances of adenomatoid tumours, diagnostic problems may arise in differentiation between the Sertoli or Leydig cell tumours, liposarcoma, mesothelioma, yolk sac tumours, and metastatic adenocarcinoma. In the confounding cases, immunohistochemical confirmation with mesothelial - related markers (calretinin, CK5/6 and WT - 1) is used to distinguish adenomatoid tumours from the non - mesothelial lesions, even in the presence of infarction[3, 17,19].

In conclusion, the adenomatoid tumours are uncommon lesions that may cause a clinical dilemma, especially when the location is intra - testicular. Preoperative imaging studies remain rather unhelpful in differentiating between the benign and malignant lesions. Under these circumstances, a radical surgical approach is warranted. However, if a benign neoplasm is suspected, no surgery, or perhaps a modified procedure allowing for the testicular preservation, is appropriate.

Περίληψη

Οι αδενωματώδεις όγκοι του οσχέου είναι σπάνια νεοπλάσματα. Αν και μια υπόνοια διάγνωσης αυτού του τύπου μπορεί να τεθεί όταν ένα νεόπλασμα με παρόμοια χαρακτηριστικά βρεθεί στην επιδιδυμίδα, όταν εντοπίζεται στον όρχι μπορεί να προκαλέσει διαγνωστικό και θεραπευτικό δίλημμα. Στο παρόν άρθρο αναφέρουμε την εμπειρία μας με τους ενδοοσχεϊκούς αδενωματώδεις όγκους: Πέντε της επιδιδυμίδας, ένα του όρχεως και έναν που εντοπιζόταν ταυτόχρονα και στον όρχι και στην επιδιδυμίδα. Επιπλέον παρατίθεται μια επισκόπηση της βιβλιογραφίας για την καλύτερη κατανόηση αυτής της καλοήθους αλλά κλινικά σημαντικής οντότητας.

Λέξεις ευρετηριασμού

αδενωματώδης όγκος, καλοήθης όγκος της επιδιδυμίδας, ενδο - οσχεϊκό νεόπλασμα

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ORIGINAL PAPER

Rare subtypes of renal cancer: Our experience and review of the literature

Panagiotis I. Mourmouris, Iraklis Mitsogiannis, Marinos Mperdempes, Aristidis A. Karagiannis, Andreas Skolarikos
2nd Urology Department, Medical School, University of Athens, Sismanogleio General Hospital, Greece

Abstract

Collective duct carcinoma, medullary carcinoma and mucinous tubular and spindle cell carcinoma are rare entities with distinctive characteristics. The purpose of this study is to present our experience with these tumors and to review the literature about the new trends in the treatment of those rare and devastating cancers. This is a retrospective analysis of 350 patients with renal tumor from which 6 cases were diagnosed with these rare tumors. All of these patients underwent radical nephrectomy except one who underwent partial nephrectomy and one who underwent radical nephroureterectomy. The mean age was 59,66 (ranging from 24 - 76) while the mean tumor size was 5,08 (range 2 - 9 cm). The mean values of Hct, γGt, SGOT and SGPT at presentation were 38,41(range 35,2 - 40,9), 22.0 (range 12 - 41), 18,33 (range 7 - 44) and 19,0 (9 - 36). Three of the patients had positive lymph nodes as histology confirmed and all of the patients but one died from their disease. These rare carcinomas are highly aggressive tumors which are not controlled with resection and despite adjuvant treatment usually have bad prognosis especially if they are presented with metastases.

Introduction

Collective duct or Bellini duct carcinoma is a relatively rare subtype of RCC, accounting for less than 1% of all RCC whereas renal medullary carcinoma is a subtype of RCC (renal cell carcinoma) that has been described relatively recently and is almost exclusively in association with sickle cell trait[1]. Collecting duct carcinomas are derived from the medulla, but many are infiltrative and extension beyond the medulla is common[2]. Most reported cases in the literature have been high grade, advanced disease, symptomatic at presentation and not responding in conventional treatment[3]. On the other hand renal medullary carcinoma (RMC) is thought to arise from the calyceal epithelium but in most cases it is highly infiltrative[4]. This subtype of RCC shares many histologic features with collecting duct carcinoma and some authors have proposed it as a subtype of the last[5]. The patients are almost always advanced and metastatic at the time of diagnosis and their prognosis is bad. Sarcomatoid variants of RCC have been described in the literature but the finding of a pure sarcomatoid tumor is extremely rare[6]. Due to these results many authors tend to believe that these tumors represent poorly differentiated regions of other

Key words
Adjuvant treatment; collective duct carcinoma; mucinous tubular and spindle cell carcinoma; renal medullary carcinoma; survival

Corresponding author:
Panagiotis Mourmouris, 2nd Department of Urology, School of Medicine, University of Athens, Sismanoglio General Hospital, 1 Sismanogleiou Street, 14578 Athens, E - mail: thodoros13@yahoo.com

TABLE 1 *Preoperative characteristics of patients with rare subtypes of renal cancer*

Patient No	Sex	Location	Symptoms	Smoking	Age (years)	Hct(%)	γGt(U/l)	SGOT(u/l)	SGPT (u/l)	INR
1	F	Left	No	Yes	58	40,6	41	13	14	1,07
2	F	Right	Yes	Yes	76	40,9	20	19	21	1,1
3	M	Right	Yes	Yes	24	37,8	20	14	23	1,35
4	M	Right	Yes	No	73	35,2	29	44	36	0,93
5	M	Right	Yes	No	60	36,0	12	7	9	1,0
6	M	Right	No	Yes	67	40,0	10	13	11	0,8

TABLE 2 *Surgery type and tumor characteristics of patients with rare subtypes of renal cancer*

Patient No	Surgery Type	Histological Type	Tumor Size(cm)	CKH	CK7	EMA	Vimentin	CK20	CKL	Stage (TNM)	Lymph Nodes
1	RN	Mucinous Tubular and spindle cell carcinoma	5,5	N/A	Positive	N/A	N/A	Negative	N/A	T1b	No
2	RNUx	Bellini Duct Carcinoma	2,0	Positive	Positive	Positive	Negative	Positive	N/A	T3a	Yes
3	RN	Medullary Carcinoma	6,0	N/A	Positive	Positive	Positive	Positive	N/A	T3b	Yes
4	RN	Bellini Duct Carcinoma	5,0	Positive	Positive	Positive	Negative	Positive	N/A	T1b	No
5	RN	Sarcomatoid	9,0	Negative	Positive	Positive	Positive	N/A	Positive	T4	Yes
6	PN	Bellini Duct Carcinoma	3,0	Positive	Positive	Positive	Negative	Positive	N/A	T1a	No

RCC types and not an independent entity[7]. Either way these tumors have an aggressive course and the medial survival is less than 1 year. Mucinous tubular and spindle cell carcinoma is an uncommon and recently described variant of renal cell carcinoma and it is associated with the loop of Henle. In our study we present our experience with these tumors and we review the literature concerning these rare tumors and their physical course.

Methods

Between years 2005 and 2014, 6 cases were diagnosed with these rare tumors. All of these patients underwent radical nephrectomy except one who underwent partial nephrectomy and one who underwent radical nephroureterectomy. We evaluated the physical course of their illness retrospectively. All of these patients were diagnosed with a renal tumor with the use of Computed Tomography (CT). After the surgery and their histological diagnosis all patients but one were referred to an oncologist.

Results

When assessing the patients characteristics (**Table 1**), we found that 4 out of 6 patients were smokers and the mean age was 59,66 (ranging from 24 - 76). 4 out of 6 patients complained about symptoms at presentation (3 presented with hematuria and 1 with mild flank pain and hematuria). The mean values of Hct, γGt, SGOT and SGPT at presentation were 38,41 (range 35,2 - 40,9), 22.0 (range 12 - 41), 18,33 (range 7 - 44) and 19,0 (9 - 36) respectively with no laboratory signs of paraneoplasmatic syndrome. Four of those patients underwent radical nephrectomy and in three of them lymph nodes were found intraoperatively enlarged and were excised. One patient underwent radical nephroureterectomy as CT findings were in favor of an urothelial cancer and the patient had positive urine cytology for urothelial cancer. One patient underwent partial nephrectomy in which a biopsy was undertaken from the surgical bed which showed positive surgical margins, which followed another sample from a wider excision which was eventually negative for cancer.

TABLE 3	*Survival rates of patients with rare subtypes of renal cancer*
Patient No	Survival (months)
1	Alive
2	9
3	8
4	18
5	5
6	14

The mean tumor size was 5.08 (range 2 - 9 cm) and in 3 patients the histology confirmed a Bellini duct carcinoma whereas in one patient the diagnosis was renal medullary carcinoma, in one patient a sarcomatoid variant of renal cell with a few areas of clear cell carcinoma and in one patient mucinous tubular and spindle cell carcinoma was diagnosed. The stage of the cancer of these patients along with the tumor characteristics are shown in **Table 2.** Three of the patients had positive lymph nodes as histology confirmed. The survival rates are shown in **Table 3**.

Discussion

Collecting duct carcinoma (CDC) is extremely rarely localized[8] but there are sparse data in the literature that report such isolated cases with long term survival, even after a partial nephrectomy[9]. The role of adjuvant treatment is such cases is unknown. On the other hand due to the invasive nature of CDC tumors when these patients are reaching an urologist they have already advanced disease. Metastasis to different organs and structures especially the bones have been reported[10]. The data that we have in order to access the survival rate of this devastating tumor are only for case reports or small trials and does not exceed 1 - 3 years with median range 30 months[11]. To date, the largest case series (n= 81) to consider outcome showed that regional lymph node metastases were present in 44% of patients at diagnosis and distant metastases were present in 32%. The survival rate was 48% at 5 years and 14% at 10 years[12,13]. These tumors may extend into the renal pelvis and on imaging studies may mimic pelvic urothelial carcinoma and this was the case with second of our patients[14]. The role of adjuvant therapy in treating these tumors is controversial. According to a recent meta - analysis which included 3 relevant studies of total 72 patients, a gemcitabine - cisplatin or carboplatin regimen gives a 26% objective response rate in 23 patients with metastatic CDC, but MVAC (methotrexate - vinblastine - doxorubicin - cisplatin) regimen achieved no response. Same study implies that immunotherapy (IFN - α, IFN - γ, and IL - 2) is not effective in treating metastatic CDC15. Finally a recent study tried to answer the question if there is a role for targeted therapies in treating CDC. In this study of 7 patients 4 patients were treated with sorafenib, 2 with temsirolimus and 1 with sunitinib. Two of these patients achieved an overall survival time accounting for 49 and 19 months, respectively but none of these patients were alive at 5 years[16].

Despite the fact that renal medullary carcinoma (RMC) affects almost exclusively men with sickle cell trait, there are case reports in the literature reporting MC in men without this disease[17]. Metastatic disease is seen at presentation in 95% of patients, with metastases in lymph nodes, lungs, liver and adrenal glands and bones[18], with median survival 5 months. This tumor type has a poor prognosis[19] and cannot be controlled only with surgery[20]. They adjuvant chemotherapy with MVAC has shown some promising results, prolonging survival for several months[21,22], even with achieving complete remission with carboplatin, gemcitabine, and paclitaxel[23]. Even with these regiments the patients eventually will become refractory and succumb to their illness. The role or radiation in treating RMC is not clarified but there are data in the literature confirming that the tumor may be radiosensitive but due to the rarity of this tumor, it is unlikely that a randomized trial can be carried out in a timely fashion in order to answer these questions[24].

In the largest series in the literature concerning sarcomatoid differentiation, the incidence of the above was found to be 8% in conventional (clear cell) renal carcinoma, 3% in papillary renal carcinoma, 9% in chromophobe renal carcinoma, 29% in collecting duct carcinoma, and 11% in unclassified renal cell carcinoma with these changes tend to present at a more advanced stage and carry a worse prognosis[25]. These tumors have a high incidence of metastases to the lungs and bones at presentation[26]. A relatively large study enrolled 63 patients from whom 34 patients received targeted therapy as the first treatment, 20 patients received cytokine therapy including interferon (19 patients) and

interleukin - 2 (1 patient)and nine patients received miscellaneous therapies, including gemcitabine or novel agents/programs in clinical trials. Five patients (8%) achieved objective responses; 4 partial responses (PRs) were observed to sunitinib therapy and 1 PR to interferon therapy whereas 30 patients achieved stable disease. The authors concluded that metastatic sarcomatoid RCC is associated with a poor response to systemic therapy[27]. The use of the combination of gemcitabine and doxorubicin may be an alternative with very low evidence though[28].

Mucinous tubular and spindle - cell carcinoma is more usually found in women. An association with nephrolithiasis and a low malignant potential has been reported in the literature[29]. The great majority of these tumors behave in a low grade fashion. There are only a few case reports demonstrating lymph node involvement[30]. Distant metastases are very rarely reported and these reports consisted of tumors with sarcomatoid differentiation. This type of RCC is well controlled with surgery and usually need no adjuvant treatment.

Περίληψη

Το καρκίνωμα εξ' αθροιστικών σωλαναρίων, το μυελοειδές καρκίνωμα του νεφρού, και το βλεννώδες σωληναριακό εξ' ατρακτοειδών κυττάρων καρκίνωμα του νεφρού είναι σπάνιες οντότητες με ιδιαίτερα χαρακτηριστικά. Ο σκοπός της παρούσας μελέτης είναι να παρουσιάσει την εμπειρία μας με αυτούς τους όγκους και να ανασκοπήσουμε την βιβλιογραφία σχετικά με τις νέες τάσεις στη θεραπεία αυτών των σπάνιων και καταστροφικών μορφών καρκίνου. Πρόκειται για μια αναδρομική ανάλυση 350 ασθενών με όγκο νεφρού από τους οποίους αναγνωρίστηκαν 6 περιπτώσεις με αυτούς τους σπάνιους όγκους. Όλοι αυτοί οι ασθενείς υποβλήθηκαν σε ριζική νεφρεκτομή, εκτός από έναν που υποβλήθηκε σε μερική νεφρεκτομή και έναν που υποβλήθηκε σε ριζική νεφροουρητηρεκτομή. Η μέση ηλικία ήταν 59,66 (εύρος 24 - 76), ενώ το μέσο μέγεθος του όγκου ήταν 5,08 (εύρος 2 - 9 cm). Οι μέσες τιμές του αιματοκρίτη, γGT, SGOT και SGPT κατά την εισαγωγή ήταν 38,41 (εύρος 35,2 - 40,9), 22,0 (εύρος 12 - 41), 18,33 (εύρος 7 - 44) και 19,0 (9 - 36). Τρεις από τους ασθενείς είχαν διηθημένους λεμφαδένες, και όλοι εκτός από έναν κατέληξαν από την νόσο τους. Αυτά τα σπάνια καρκινώματα είναι πολύ επιθετικοί όγκοι που δεν ελέγχονται με χειρουργική εκτομή και παρά την επικουρική θεραπεία συνήθως έχουν κακή πρόγνωση ειδικά αν παρουσιάζονται με μεταστάσεις.

Λέξεις ευρετηριασμού

Καρκίνωμα εξ' αθροιστικών σωλαναρίων, Μυελοειδές καρκίνωμα του νεφρού, βλεννώδες σωληναριακό εξ' ατρακτοειδών κυττάρων καρκίνωμα, επικουρική θεραπεία

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ORIGINAL PAPER

Reconstructive urethral surgery for anterior urethral strictures: A preliminary experience in a referral single center in Cyprus

Dimitris Costi[1], Guido Barbagli[2], Sofia Balò[2], Massimo Lazzeri[2], Athina Mavrou[1]
[1] Evangelistria Medical Centre, Nicosia, Cyprus
[2] Centro Chirurgico Toscano, Arezzo, Italy

Abstract

Introduction: We report our preliminary experience and the results of different types of urethroplasties to repair anterior urethral stricture in a referral single center in Cyprus.
Materials and methods: We performed a retrospective descriptive analysis of a cohort of patients who underwent anterior urethroplasty between October 2012 and October 2014 at the Center for Reconstructive Urethral Surgery in Nicosia, Cyprus.Inclusion criteria included patients who underwent anterior one - stage or two - stage urethroplasty. Patients with posterior urethral strictures or incomplete clinical records at followup analysis were excluded from study. The primary outcome of the study postoperative failure - free survival in the overall population. The objective outcome was considered a failure when any post - operative instrumentation was needed, including dilation.
Results: A total of 18 patients were considered eligible for review according to the inclusion/exclusion criteria. Median patient age was 40 years (range 22 - 70).All patients underwent one - stage repair using oral mucosal graft. With amedian follow - up of 11 months (range 1 to 25), no patients develop recurrence of stricture.
Conclusions: One - stage urethroplasty with oral mucosa provide excellent results in a limited series of patients showing different penile and bulbar stricture diseases.

Introduction

Reconstructive urethral surgery has greatly improved in safety, variety and effectiveness during the last 3 decades[1]. Although endoscopic treatment can transiently improve urinary flow, open urethroplasty is now regarded as the gold - standard treatment for anterior and posterior urethral strictures[2]. Numerous surgical techniques have been suggested to repair anterior urethral stricture and there the long - term results with more than 7 - 10 years of followup in large series of patients are available in the literature[3 - 6].

Key words
urethra; stricture; urethroplasty; oral mucosa

We report our preliminary experience and the results of different types of urethroplasties to repair anterior urethral stricture in a referral single center in Cyprus.

Corresponding author:
Dimitris Costi, M.D., Evangelistria Medical Centre, 1, M. Gergallia Str, 1095 Nicosia, Cyprus
Tel. 22 410 100; Fax: 22 670 363, E - mail: dimcosti@gmail.com

Materials and methods

We performed a retrospective descriptive analysis of a cohort of patients who underwent anterior urethroplasty between October 2012 and October 2014 at the Center for Reconstructive Urethral Surgery in Nicosia, Cyprus. The cutoff date for the analysis was December 31, 2014. The last followup for each patient reflects the last point of contact with the office. Followup was calculated for each patient based on time from surgery to the last office followup. The study was approved by the institutional review board. Inclusion criteria included patients who underwent anteriorone - stage or two - stage urethroplasty. Patients with posterior urethral strictures or incomplete clinical records at followup analysis were excluded from study. The primary outcome of the study postoperative failure - free survival in the overall population.Preoperative evaluation included clinical history, physical examination, urine culture, residual urine measurement, uroflowmetry, urethrography, urethral ultrasound and urethroscopy. Patients with meatal/navicularis strictures underwent calibration of the meatus using progressive Nelaton catheters 8,10.12 F. The objective outcome was considered a failure when any post - operative instrumentation was needed, including dilation. Uroflowmetry and urine culture were repeated every 4 months in the first year and annually thereafter. When symptoms of decreased force of stream were present and the uroflowmetry was less than 12 ml per second, urethrography, urethral ultrasound, urethroscopy and meatal calibration were repeated.In all patients, the oral mucosa was harvested from the cheek according to our current surgical technique[7].

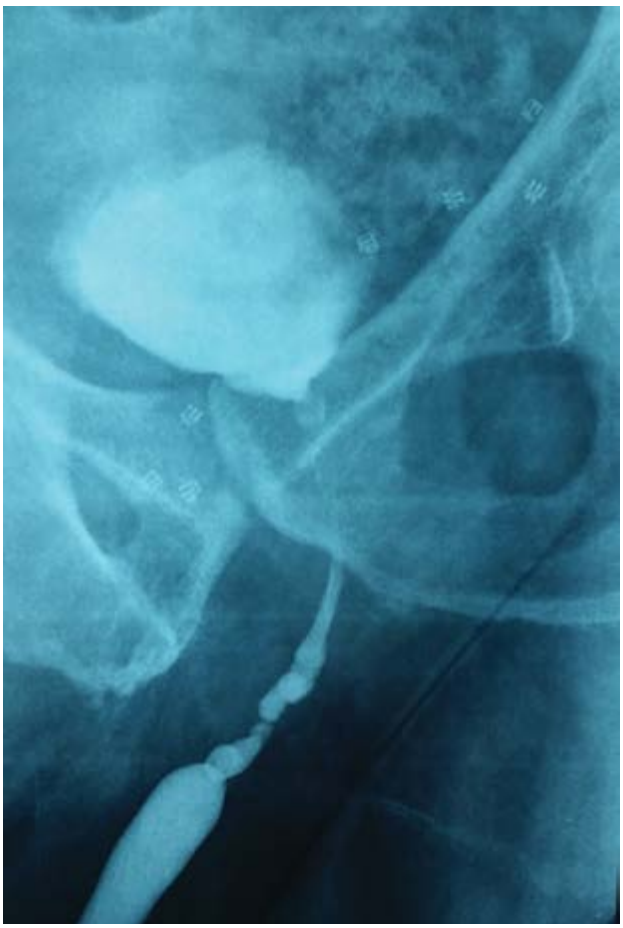

Figure 1. *Pre - operative urethrography showing long complex bulbar urethral sticture. Intraoperatively appeared few mm from the external sphincter*

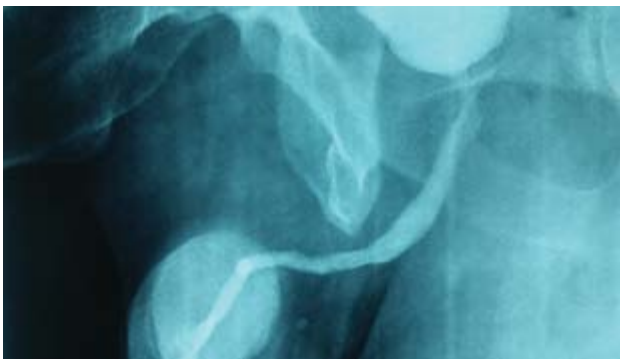

Figure 2. *Post - operative urethrography showing a regular penile and bulbar tracts after vental oral mucosal graft urethroplasty (Barbagli's procedure)*

Surgical techniques

Combined graft - flap urethroplasty

The urethral mucosa involved in the disease was completely removed from the meatus to the tip of the glans. A graft of oral mucosa was sutured to substitute the urethral mucosa. Rectangular longitudinal flap was designed on the ventral surface of the penile skin and sutured over the oral graft. A Foley 12 Fr. silicone catheter was left in place for 2 weeks.

Asopa's urethroplasty

The urethra was longitudinally opened and the urethral plate was fully exposed. A Snodgrass's incision was made on the urethral plate to create a wide window. The oral graft was sutured to the window on the urethral plate and the urethral was tubularized over 12 Fr. Foley silicone catheter.

TABLE 1 *Stricture etiology in patients with anterior urethral strictures*

Etiology	No. patients (%)
catheter	4 (22.2%)
instrumentation	4 (22.2%)
lichen sclerosus	3 (16.7%)
failed hypospadias repair	3 (16.7%)
idiopathic	2 (11%)
congenital	1 (5.6%)
infection	1 (5.6%)
TOTAL	18

TABLE 2 *Stricture site*

Site	No. patients (%)
meatus - navicularis	6 (33.3%)
penile	2 (11.1%)
bulbar	8 (44.4%)
pan - urethral	2 (11.1%)
TOTAL	18

TABLE 3 *Stricture length*

Length	No. patients (%)
1 - 2 cm	1 (5.6%)
2 - 3 cm	7 (38.9%)
3 - 4 cm	3 (16.7%)
4 - 5 cm	5 (27.8%)
pan - urethral	2 (11%)
TOTAL	18

TABLE 4 *Previous treatment in patients with anterior urethral strictures*

Previous treatment	No. patients (%)
none	1 (5.6%)
dilation	4 (22.1%)
urethrotomy	10 (55.5%)
meatotomy	1 (5.6%)
urethroplasty	1 (5.6%)
associated treatments	1 (5.6)
TOTAL	18

TABLE 5 *Type of urethroplasty performed in patients with anterior urethral strictures*

Stricture Site	No. patients	Type of urethroplasty
meatus - navicularis	6	3 Asopa 3 graft + flap
penile	2	2 Asopa
bulbar	8	6 ventral 2 Asopa
panurethral	2	1 ventral + Asopa 1 ventral
TOTAL	18	

Ventral graft urethroplasty

The bulbar urethra was exposed and longitudinally opened along its ventral surface. The oral graft is sutured to the urethral mucosa and the spongiosum tissue is sutured over the graft. A Foley 16 silicone catheter is left in place for 4 weeks.

Results

A total of 18 patients were considered eligible for review according to the inclusion/exclusion criteria. Median patient age was 40 years (range 22 - 70). In the majority of patients, the stricture etiology was caused by catheter (22.2%) or urethral instrumentation (22.2%) **(Table 1).**

The stricture involved the distal urethra (meatus and navicularis tract) in 6 (33.3%) patients, the penile urethral in 2 (11.1%), the bulbar urethra in 8 (44.4%) and the anterior urethra for its entire length (pan - urethral stricture) in 2 (11.1%) **(Table 2).**The urethral stricture length ranged from 1 to 5 cm and 2 patients showed pan - urethral strictures**(Table 3).**Only 1 patient (5.6%)% had not had any previous treatment and the majority of patients undergone previous failed urethrotomy (55.5%) or periodic dilation (22.1%) **(Table 4).** All patients underwent one - stage repair using oral mucosal graft. The surgical techniques are summarized in **Table 5.** With amedian follow - up of 11 months (range 1 to 25), no patients develop recurrence of stricture.

Discussion

Our survey herewith confirm that one - stage reconstruction of anterior urethra using oral mucosal graft is successful in a large series of patients.We

mainly used the transplant of the graft as an inlay inside the urethral plate as described by Asopa in 2001 or as an only in the ventral bulbar urethral surface as described by Morey and McAninch in 1996 and revisited by Barbagli et al. in 2013[8,9,10]. Using only three different techniques we were able to repair 18 different urethral stricture diseases. In two patients presenting panurethral stricture involving all the penile and bulbar urethra we combined the Asopa's technique, we used for penile urethroplasty, with the ventral onlay graft technique we used for bulbar urethroplasty.

The main limitation of our study is the small number of patients here reported (18 cases) and the short followup (median 11 months). Considering the current life expectancy in Western countries, failures could be detected after 20 years and our observation time may be considered short using such as comparison.[7] Furthermore, as reconstructive urology continues to evolve, the definition of failure and methodologies to assess urethral integrity are becoming increasingly important to enable us to compare future studies.[7]

Conclusions

One - stage urethroplasty with oral mucosa provide excellent results in a limited series of patients showing different penile and bulbar stricture diseases.

Περίληψη

Εισαγωγή: Η επανορθωτική χειρουργική της ουρήθρας έχει βελτιωθεί σημαντικά τόσο στην ασφάλεια, όσο και στην ποικιλία και στην αποτελεσματικότητα κατά τις τελευταίες τρεις δεκαετίες. Μόλονότι η ενδοσκοπική θεραπεία μπορεί να βελτιώσει παροδικά τη ροή των ούρων, η ανοιχτή ουρηθροπλαστική θεωρείται πλέον ως θεραπεία πρότυπο για τα στενώματα της πρόσθιας και οπίσθιας ουρήθρας. Αρκετές χειρουργικές τεχνικές έχουν προταθεί για την διόρθωση του στενώματος της πρόσθιας ουρήθρας και μακροπρόθεσμα αποτελέσματα με περισσότερα από 7 - 10 έτη σε follow up μεγάλων σειρών ασθενών είναι διαθέσιμα στη διεθνή βιβλιογραφία. Σκοπός του άρθρου είναι να παρουσιάσει τα προκαταρκτικά αποτελέσματα των διαφόρων τύπων ουρηθροπλαστικής στην αντιμετώπιση στενωμάτων της πρόσθιας ουρήθρας και την εμπειρία ενός μόνο κέντρο στην Κύπρο.

Υλικά και μέθοδοι: Πραγματοποιήσαμε μια αναδρομική περιγραφική ανάλυση μιας σειράς ασθενών που υποβλήθηκαν σε πρόσθια ουρηθροπλαστική μεταξύ του Οκτωβρίου του 2012 και Οκτωβρίου του 2014 στο Κέντρο Επανορθωτικής χειρουργικής της ουρήθρας στη Λευκωσία. Η μελέτη περιελάμβανε ασθενείς που υποβλήθηκαν σε πρόσθια ουρηθροπλαστική σε ένα ή δύο στάδια. Ασθενείς με στενώματα της οπίσθιας ουρήθρας, ασθενείς με ελλιπή κλινικά στοιχεία ή ανεπαρκές follow up αποκλείστηκαν από τη μελέτη. Το πρωτεύον καταληκτικό σημείο της μελέτης ήταν η μετεγχειρητική ελεύθερη αποτυχίας επιβίωση στον συνολικό πληθυσμό. Ως αποτέλεσμα στόχος θεωρήθηκε η αποτυχία η οποία ορίστηκε ως η ανάγκη χρήση οποιουδήποτε όργανου μετεγχειρητικά, συμπεριλαμβανομένης δε και της διαστολής.

Αποτελέσματα: Συνολικά 18 ασθενείς θεωρήθηκαν επιλέξιμοι για ανασκόπηση σύμφωνα με τα κριτήρια ένταξης / αποκλεισμού. Η διάμεση ηλικία των ασθενών ήταν 40 έτη (εύρος 22 - 70) .Όλοι υποβλήθηκαν σε αποκατάσταση ενός σταδίου με τη χρήση μοσχεύματος απο το στοματικό βλεννογόνο. Σε ενδιάμεσο διαστημα παρακολούθησης των 11 μηνών (εύρος 1 - 25), κανένας από τους ασθενείς δεν ανέπτυξε υποτροπή της στένωσης.

Συμπεράσματα: Η πρόσθια ουρηθροπλαστική με χρήση στοματικού βλεννογόνου σε ένα στάδιο παρείχε εξαιρετικά αποτελέσματα σε μια περιορισμένη σειρά ασθενών με στένωση.

Λέξεις ευρετηριασμού
στένωμα ουρήθρας, ουρηθροπλαστική, στοματικός βλεννογόνος

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CASE REPORT

Penile fracture in a 65 - year old man: Combined approach with conservative treatment and delayed surgical repair

Aristomenis Gekas[1], Panagiotis Kartsaklis[2], Charalampos Konstantinidis[3], Panagiotis Politis[1], Charalampos Thomas[4], George Tsamboukas[1], Vasileios Vossos[5]
[1]Department of Urology, General Hospital of Patras, [2]Urologist, Zakynthos, [3]Urology and Neuro - urology Unit, National Rehabilitation Center, [4]Urologist, Corinthos, [5]Department of Urology, General Hospital of Agrinio

Abstract

Introduction: Penile fracture is a relatively uncommon urologic emergency, happening mainly during coitus. Although it occurs in young males, our case demonstrates that competent, elderly men are also affected.
Case report: A 65 year old man presented with the typical history of a penile fracture. Physical examination showed a painful, swollen, ecchymosed penis. Since the involvement of urethra was considered unlike, the patient underwent to a combined conservative and surgical treatment.
Conclusion: A combination of conservative and surgical treatment offered equal results with the immediate approach. The patient preserved his potency, reporting no pain or deviation 2 months after the surgery.

Introduction

Penile fracture is considered to be a rather infrequent event in the list of urologic emergencies. Sometimes, due to the violent manipulation during erection, tunica albuginea is unable to tolerate the high intracorporeal pressure and is ruptured. The result is the creation of a localized or diffuse hematoma which in case of Buck's rupture is expanded in the scrotum and the lower abdominal wall. Urethra may be affected if corpora spongiosum is involved[1].

The diagnosis of a penile fracture is mainly clinical and is based on physical history and examination. Most of the patients report a violent deviation of the penis during coitus or other manipulation, resulting in acute pain, loss of erection and a rapid expanding swelling of the penile shaft. Hematuria, difficulties in urination or bloodstain from the meatus implicate involvement of the urethra, condition which demands rapid evaluation[2].

Key words
Penile fracture; conservative treatment; surgery; combined treatment

Surgical correction consists of evacuating the hematoma, closing the defect of the tunica albuginea and the Buck's fascia, as well.

In case of urethra involvement,

Corresponding author:
Tsamboukas George, E - mail: tsampoukasg@gmail.com

Figure 1. *Presentation of the penile fracture, a few hours after the event*

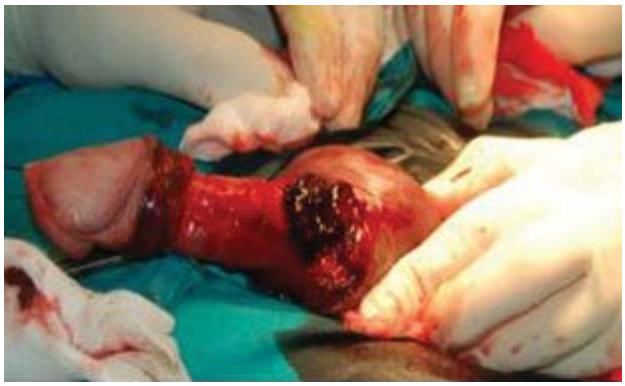

Figure 2. A*n hematoma was recognized overlying the rupture, at 3 o' clock time*

urethroplasty must be performed simultaneously with the correction of the corpora cavernosa's wound [3].

Although is considered to be a condition of young males, elderly should also not be excluded. In this case, we present a 65 years old male who arrived in the emergency room referring a recorded but rather infrequent cause of injury. The patient underwent delayed exploration and successful repair of his injury.

Case presentation

We report the case of a 65 - year - old male who presented to the emergency department a few hours after a blunt self - injury of his penis. Specifically, the patient said that he had tried to put his erected penis back into his underwear in order to go void; a "cracking" - sound was then followed by a rapid detumescence and severe penile pain. Nevertheless, the patient said that he had voided well several times, reporting no hematuria.

Physical examination revealed a flaccid and entirely swollen penis, totally ecchymosed from the pubic symphysis up to the prepuce. In the ventral aspect the swelling was found up to the scrotum.

The urethral meatus could not be seen due to the swollen prepuce, but no blood tearing was observed. A Tiemman catheter was placed successfully in blind **(figure 1)**. The patient denied underlying diseases and he reported no co - existent Peyronie's disease, a previously otherwise healthy penis, aesthetically and functionally. He was admitted in our hospital and the appropriate diagnosis for penile fracture led to careful management scheduling.

Treatment

Initially, the patient received conservative treatment with antibiotics and anti - inflammatory drugs.

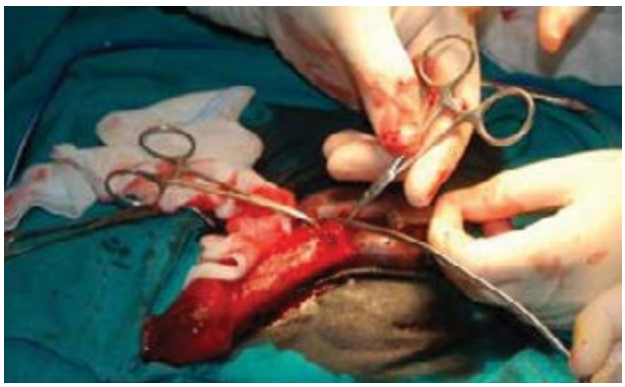

Figure 3. *The defect of the wound was closed with interrupted absorbable sutures 3 - 0*

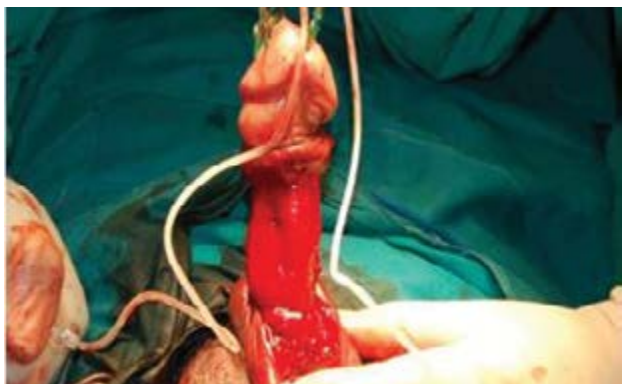

Figure 4. *The artificial erection confirmed the correction, showing no leakage and no deviation of the penis*

Approximately 2 days after the event, the man was scheduled for a surgical exploration and repair.

A sub coronal, circumcision - like incision was made. The penis was degloved up to the penoscrotal junction. A hematoma in the left aspect of the penis was recognized **(fig. 2)** and was evacuated. The rupture of corpora cavernosa was found, at 3 o'clock position. Buck's fascia was also ruptured in an unclear manner. Corpus spongiosum was found intact. A folley catheter No. 16

was placed. The rupture of tunica albuginea was then closed in an interrupted manner, with 3 - 0 absorbable sutures. The Buck's fascia was used to cover the site of the rupture and was also closed with interrupted absorbable 3 - 0 sutures, in order to avoid multiple knots sensation. An artificial erection with saline injection into the glans was performed in aim to confirm the correction of the leakage and rule out over - treatment which could have led to penile deviation **(fig. 4)**.

A circumcision was performed, in order to free the penis from the swollen prepuce and to optimize the final result. The patient was hospitalized for 4 days in order to ensure no further complications due to his advanced age, receiving antibiotic, anti - inflammatory and anti - androgenic therapy, for suppression of his erections. He was counseled to avoid any sexual intercourse for 1 month.

Results

The patient was examined 2 months after the discharge. He reported preserved potency with intercourse 8 weeks postoperatively, no postoperative penile curvature or pain during erection.

Discussion

The etiology of the penile fracture depends on geographical criteria, since in Western World the main reason is the sexual intercourse, while in Eastern World "Taghaandan" (a manipulation of the erect penis to achieve detumescence) is considered as the main cause of blunt penile injury[4]. The contemporary injury of the urethra is also extremely low in the Persian Gulf and Japan and to up to 38% in the U.S. and Europe, pointing out the relation of the complicated penile fracture with sexual intercourse[1]. Since seeking of medical attention for such a reason often causes embarrassment or fear, the true incidence is greater than the number reported in the literature[4]. In our case, the patient reported an uncommon clumsy manipulation which led to the penile injury.

The thinning of the tunica albuginea and the increase of intracavernous pressure during abrupt loading or bending of the penis is known to be responsible for such injuries[5]. In addition, during age the ratio collagen/elastin fiber in the tunica is increased, by making tunica less compliant and more prone to injuries[6]. Even we have no tactile evidences for that in this case, we could assume that our elderly patient might have an extra risk factor.

The history and physical examination clearly pointed out a penile fracture[7]. Thus, considering this a typical case, there was no need for further imaging exploration, like ultrasound of the penis, cavernosonography or MRI in order to establish the diagnosis[8]. The absence of a bloodstain from the urethral meatus and the unreported dysuria or hematuria till the arrival in the ERs excluded the possibility of a urethra's rupture and the need for an antergrade urethrography[3].

As far as the therapeutic approach is concerned, we chose an initial short - term conservative treatment of 2 days with anti - inflammatory drugs and antibiotics, followed by the final surgical exploration. The first one aimed to the avoidance of the acute stage of trauma, allowing the extensive edema and hematoma to be reduced and stabilized, making clear the position of the rupture and offering us a more clearly visible surgical field. The surgery offered the opportunity of the final correction of the injury, keeping away the possible sequelaes of conservative treatment, such as expanded or infected hematoma, abscess formation, severe penile angulations, arteriovenous fistulas or Fournier's Gangrene[8].

In addition, the actualization of surgical repair >24 hours after the presentation did not worry the surgery team, as the literature does not report differences in rates of ED or other complications, between immediate and delayed repair. Specifically, in their systematic review, Wong et al.[9], analyzed 10 retrospective observational comparative studies of immediate versus delayed surgical correction of penile fractures. The delayed groups had a mean time to repair ranging from 29 hours to 16 days, while the immediate correction was considered correction within 24 hours. Amongst these two groups, the complications of ED, plaque or curvature did not differ significantly, a conclusion that render delayed repair as a "reasonable alternative to immediate surgery". Considering that, we can assume that as long as the definitive approach of a penile fracture remains the surgical correction of it within a reasonable interval - which still remains a debate - , the time itself does not makes things worse.

As a technique, we chose the subcoronal circumferential approach and the degloving of the penis. In spite of alternatives techniques such as direct

longitudinal incision over the injury, inguino - scrotal approach, midline incision of the raphe, suprapubic approach[10], we strongly advocate penile degloving because it offers excellent exposure of the 3 corporas, which apprehend any urethral or tunica injuries that have been eluded of the evaluation. We used absorbable sutures, contrary to the most common used Nylon sutures[7], since our experience with them in Peyronie's disease repair has demonstrated excellent results.

Conclusions

In our case, the combination of conservative and surgical treatment was proved to be equally effective with the standard immediate approach of a penile fracture, reproducing the reports of the literature. The age of our patient did not alter our approach to the case and did not seem to affect the outcome as well. Finally, we advocate the subcoronal circumferential incision as the most trustworthy approach for the repair of a penile fracture.

Περίληψη

Εισαγωγή: Το κάταγμα του πέους αποτελεί ένα ασύνηθες επείγον ουρολογικό περιστατικό, το οποίο συμβαίνει κυρίως κατά τη σεξουαλική επαφή. Το παρόν περιστατικό δείχνει πως η κατάσταση αυτή, αν και συναντάται κυρίως στους νέους, αφορά και μεγαλύτερους, σεξουαλικά ικανούς άντρες.
Παρουσίαση: Άνδρας, 65 ετών, προσέρχεται στα ΤΕΠ αναφέροντας ένα τυπικό ιστορικό πεϊκού κατάγματος. Η φυσική εξέταση απεκάλυψε ένα πέος που είχε υποστεί κάταγμα, χωρίς συμμετοχή της ουρήθρας. Ο ασθενής υπεβλήθη σε συνδυασμένη, συντηρητική και σε δεύτερο χρόνο χειρουργική, θεραπεία.
Συμπεράσματα: Ο συνδυασμός της συντηρητικής και καθυστερημένης χειρουργικής θεραπείας, έναντι της πιο διαδεδομένης άμεση χειρουργικής αποκατάστασης, προσέφερε εξίσου επιτυχημένο αποτέλεσμα.

Λέξεις ευρετηριασμού
κάταγμα πέους, συντηρητική αντιμετώπιση, χειρουργείο, συνδυαστική θεραπεία

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CASE REPORT

Penis self - injection of liquid paraffin

Ioannis Solinis, Michael Platanas, Christos Mavroudis
Department of Urology, General Hospital of Didymoticho

Abstract

The injection of liquid paraffin subcutaneously for penis enlargement, although it is medically unacceptable, is still used in some countries of Eastern Europe and Far East. The complications of the technique are many and serious. We presented a case of a person, which is rare in Greece, who had carried out self - injection of liquid paraffin in the penis resulting in significant deformity and dysuria due to phimosis.

Key words
penis;
liquid paraffin;
self injection

Introduction

The use of liquid silicone, paraffin or other swelling materials to increase the tissue volume is considered a reprehensible medical practice with disastrous consequences for the body and it can even lead to death[5]. Subcutaneous injection of liquid paraffin to the penis to enlarge it and specifically to increase its thickness is a process that occurs in some countries of Eastern Europe (Russia, Bulgaria, Romania, Ukraine) and the Far East (Korea, Myanmar, Laos)[3,5]. Due to the rarity of the situation in Greece, we are presenting the case of a Bulgarian male patient, who had carried out liquid paraffin self - injection into his penis, 4 months before coming to the Outpatient Department.

Case report

A 27 year old Bulgarian came to the Emergency Clinic reporting difficult urination, which had appeared 4 months previously, when, as per his statement, he performed a liquid paraffin injection in his penis. The purpose of self - injection was the enlargement of the genital organ. He did not explain however if he had performed one or more injections. The clinical examination found a very large and partially uneven swelling of the entire penis, except for approximately 3 cm at its root. The swollen foreskin creates phimosis and it was impossible to uncover the penis balanus. There were no signs of inflammation of the specific area (pain, redness, temperature increase). The scrotum was normal. The patient's only symptom was intense dysuria justified by the phimosis. The organ's function was not discussed, as the patient had been detained from the early days of the injection and it was manifestly impossible. Also, (at the request of the patient), the quality of erection remained unclear. The routine laboratory testing (complete blood count, biochemistry, urinalysis) did not reveal any abnormality.

We proposed to the patient to perform circumcision to restore urination. Surgery was done under general anaesthesia. The excision of the swollen foreskin was particularly difficult because of its hardness due to the addition and solidification of the liquid paraffin into the tissue. The added material in the tissues was firmly connected both with the skin of the penis and

Corresponding author:
Ioannis Solinis, 49, Kalymnou Str. Alexandroupoli PC 68100,
Tel. 25510 -38612, 6932833695, E - mail: isolinis@yahoo.com

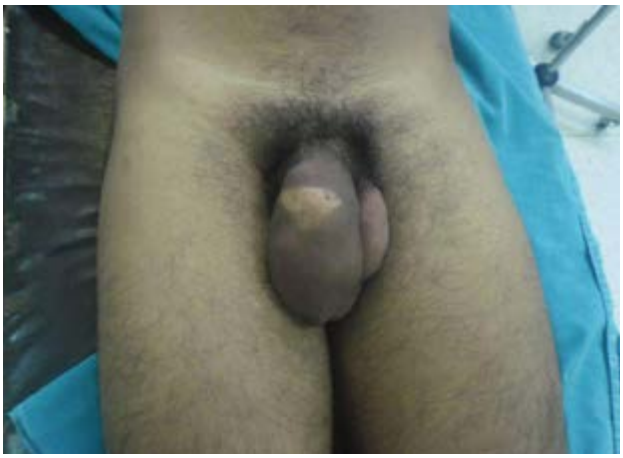

Figure 1: *Preoperative image of the swollen penis*

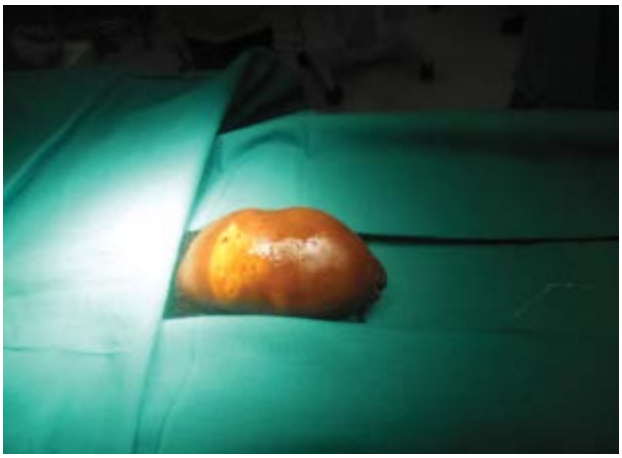

Figure 2: *Preoperative image of the expanded penis in the surgical field*

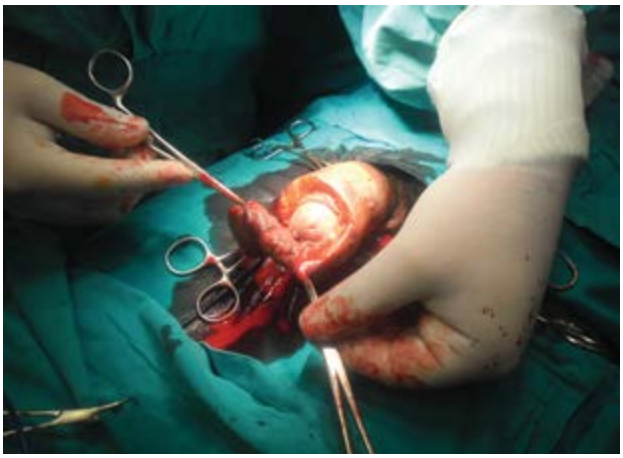

Figure 3: *Excision of the expanded foreskin*

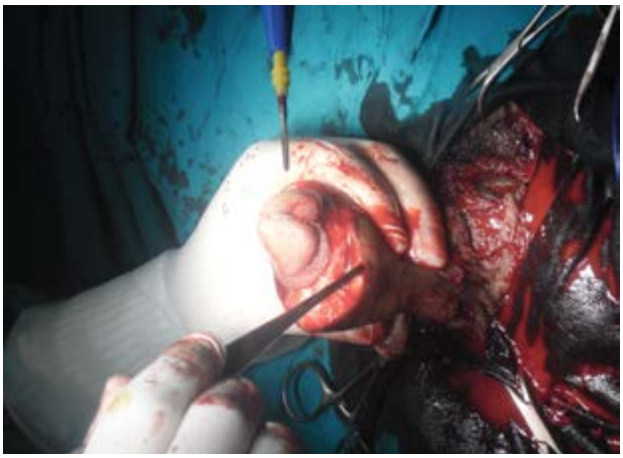

Figure 4: *Haemostasis was extremely difficult*

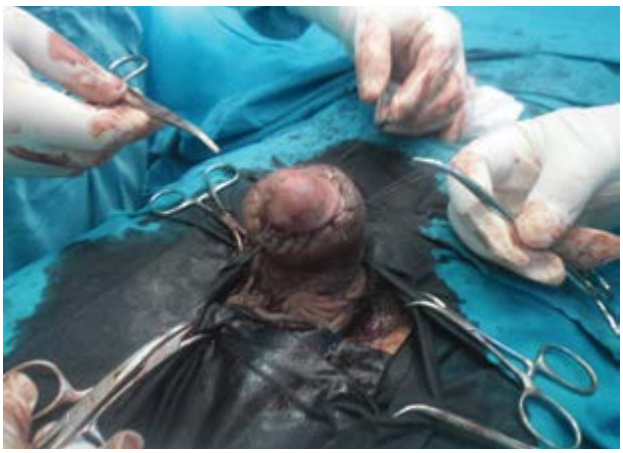

Figure 5: *Postoperative results of circumcision*

the corpora cavernosa. Haemostasis was extremely difficult. Finally, the removed foreskin was sent for histological examination.

Postoperatively, the patient reported that the quality of the urination had been fully restored. He did not present any complication and left the hospital on the 2nd postoperative day.

The histopathological report stated "reactionary and inflammatory skin lesions", while the dermis presented "moderate round cell infiltrations around optically empty spaces".

Discussion

Many men in recent years, influenced perhaps by the modern lifestyles, have been looking or seeking to increase the penile length or (most commonly) the penile circumference. Nonetheless, the often poorly informed patients are ready to proceed to unacceptable methods such as liquid paraffin injection due to the low cost and the erroneous guidance[1].

In 1899, an Austrian surgeon made an injection of vaseline to the scrotum of a patient who had

undergone bilateral orchiectomy because of tuberculous epididymitis. His aim was to replace the absence of testicles. The surgery was deemed successful and later, other substances were used for the same purpose, such as mineral oil, cod liver oil, silicone and liquid paraffin[5].

The principle of the technique was the injection of a substance in a semi - liquid state, in conditions of increased temperature and which would solidify when it became cooler. At this state it is stabilised in the human body. Thus, liquid paraffin, like other substances used in the treatment of cleft palate, urinary fistulas and inguinal hernia. Those were mostly used for cosmetic purposes such as facial wrinkles, breast augmentation and penis size enlargement[1]. Today, the use of liquid silicone is approved by the Food and Drug Administration United States (FDA) only for ophthalmic use.

Despite the serious complications reported, the technique remained popular the first two decades of the 20th century. The injection of liquid paraffin is still used in some countries of Eastern Europe and the Far East in order to enlarge the penis and specifically its circumference. It is performed either by self - injection or by persons without medical training and under unacceptable medical conditions[1].

Subcutaneous injection of liquid paraffin and the subsequent reaction with the tissues results in the creation of flat and stable nodules. This condition was initially designated by the pathological - anatomical term "sclerosing lipogranuloma". This term was used to describe histopathological features, corresponding to the replacement of normal subcutaneous tissue by cystic spaces with paraffin. Later, (after 1971) the term "paraffinoma" was introduced and is now preferred, to describe pathological findings caused by the injection of liquid paraffin or a similar material[4].

The complications of the technique reported in the literature are severe and include: deformation of the penis and phimosis, erectile dysfunction and failure of penetration, ulcers and skin necrosis, abscesses and Fournier gangrene. Tissue reaction to the injection of paraffin can be gradually increased and continue for months and even years after the injection[5]. Some incidents have been reported to be treated 20 years later and while the initial diagnosis was possible penile neoplasm[2].

The treatment of penile parrafinoma includes wide excision of the skin and underlying tissues that have been infiltrated by the foreign substance. The aim is to restore the organ cosmetically as well as functionally. Recovery operations may be complicated with techniques of both plastic and reconstructive surgery. Many a time an invasive procedure is required, with several stages that include (depending on the extent of damage) stripping the penis, burying the organ in the scrotum and recovery three months later[5]. The failure of complete excision of the foreign body and the concomitant damage can lead to a relapse resembling neoplasma. Finally, interstitial injection of corticosteroids has been reported previously with various results in selected cases.

Various studies have shown that at least 25% of men underestimate the size of their organ and do not require any surgery[3]. In these cases appropriate psychological support is recommended rather than any kind of intervention. Various techniques for increasing the penis are under investigation, but none has become a standardized urological practice[5].

Conclusion

Both medical specialists (Urologists, Dermatologists) and the public should be aware of the unscientific and totally inappropriate methods used such as liquid paraffin injection, and especially by persons without medical training. Also, they should be aware of the consequences of such techniques. The only acceptable response to such incidents is considered the complete excision of the lesion and the restoration of the organ.

Περίληψη

Η έγχυση υγρής παραφίνης υποδερματικά για τη μεγέθυνση του πέους, παρότι είναι απαράδεκτη ιατρικά, εξακολουθεί να χρησιμοποιείται σε ορισμένες χώρες της Ανατολικής Ευρώπης και της Άπω Ανατολής. Οι επιπλοκές της τεχνικής είναι πολλές και σοβαρές. Παρουσιάζεται περιστατικό, σπάνιο για τα ελληνικά δεδομένα, ατόμου που είχε διενεργήσει αυτοένεση υγρής παραφίνης στο πέος του με αποτέλεσμα σημαντική δυσμορφία και δυσουρία λόγω φίμωσης.

Λέξεις ευρετηριασμού

πέος, υγρή παραφίνη, αυτοένεση

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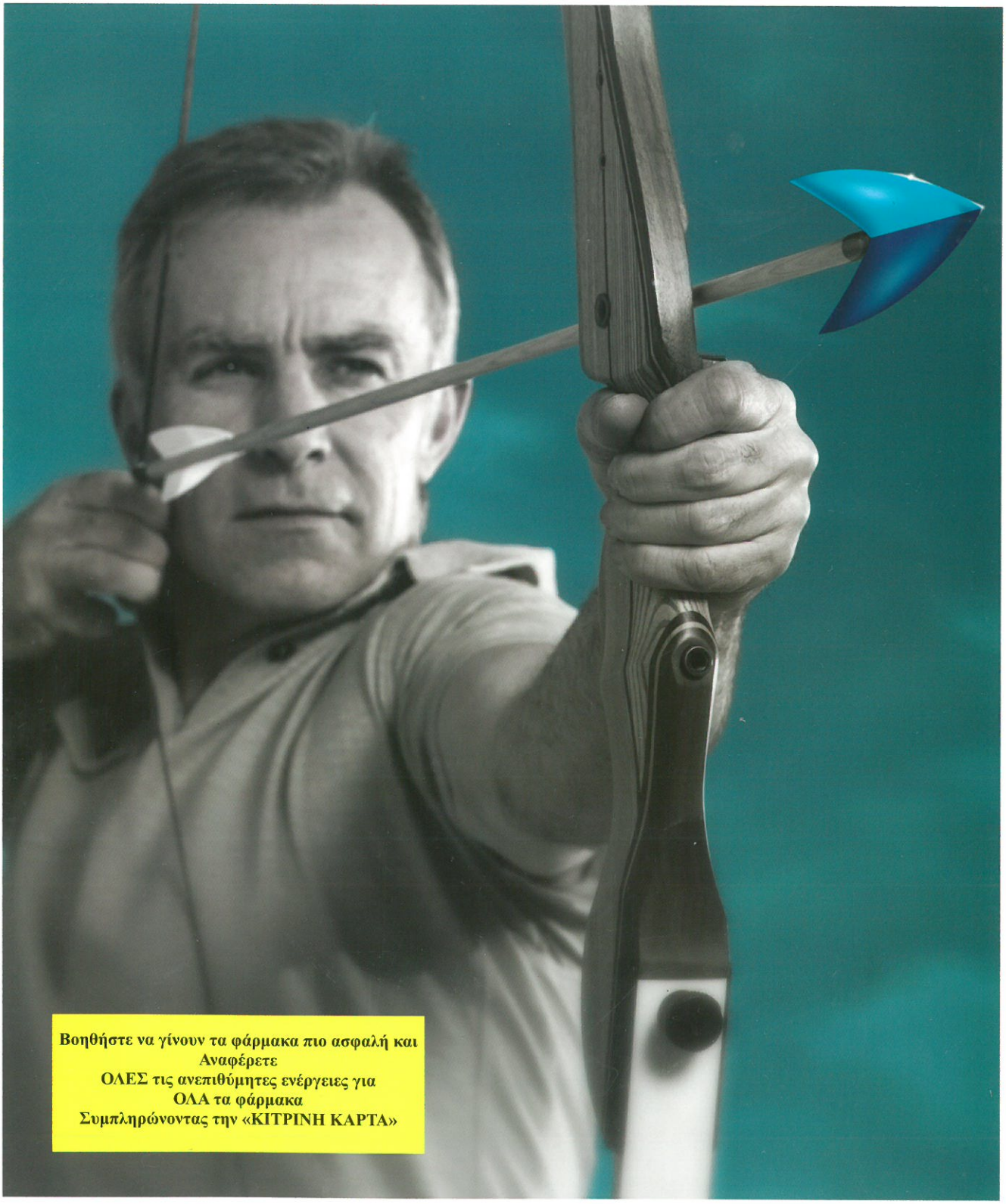

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