PENOSKROTALNA PAGETOVA BOLEST – PRIKAZ SLUČAJA I PREGLED LITERATURE

PRIKAZ SLUČAJA

CASE REPORT

PENOSCROTAL PAGET'S DISEASE – CASE REPORT AND LITERATURE REVIEW

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SAŽETAK

Uvod: Penoskrotalna Pagetova bolest je veoma retka u svetu, sa malim brojem prikaza slučajeva, te tako predstavlja veliku dilemu u dijagnostici i lečenju.

Prikaz slučaja: Muškarac starosti od 81 godine javlja se prvi put na Institut za onkologiju i radiologiju Srbije (IORS), zbog ulcerisane i eritematozne tumorske promene promera oko 10 cm prekrivene skvamoznim pločama, koja se proteže od preponske regije levo do skrotuma. Tumefakt je eritematozan, prokrvljen i povremeno krvari, a pacijent od tegoba navodi povremeni bol u levoj nozi. Prethodno je učinjena biopsija navedene tumorske promene u drugoj ustanovi, a patohistološki (PH) nalaz je išao u prilog ekstramamarnoj Pagetovoj bolesti. Pacijent je prezentovan konzilijumu IORS-a, koji je doneo odluku o operativnom lečenju.

Zaključak: Ova bolest se nalazi i izvan klinički vidljivih lezija, pozitivne ivice resekcije su česte, a to predstavlja glavni faktor rizika za recidiv bolesti. Tačna preoperativna dijagnoza i pravilno hiruško lečenje, predstavljaju adekvatno lečenje, kojim se izbegava pojava recidiva i ponovnih operacija, što je svakako ključan faktor u preživljavanju. Ovaj prikaz slučaja za onkologe svakako predstavlja značajan korak ka razumevanju ove bolesti.

Ključne reči: penoskrotalna Pagetova bolest, ivice resekcije, recidiv bolesti, adekvatno lečenje

ABSTRACT

Introduction: Penoscrotal Paget's disease is very rare worldwide, with a small number of case reports, and it thus represents a major dilemma in diagnosis and treatment.

Case report: An 81-year-old man presents himself to the Institute of Oncology and Radiology of Serbia (IORS) for the first time due to an ulcerated and erythematous tumor change about 10 cm in diameter covered with squamous plates, which extends from the groin region on the left to the scrotum. The tumefaction is erythematous, bloody and it occasionally bleeds, and the patient complains of occasional pain in the left leg. Previously, a biopsy of the mentioned tumor change was performed in another institution, and the PH finding was in favor of extramammary Paget's disease. The patient was presented to the IORS council, which decided on operative treatment.

Conclusion: This rare disease is also found outside of clinically visible lesions, positive resection margins are common, and this represents the main risk factor for disease recurrence. Accurate preoperative diagnosis and proper surgical treatment are crucial for preventing relapses and repeat operations, making them key factors in improving survival. This case report certainly represents a significant step for oncologists in understanding this disease.

Keywords: penoscrotal Paget's disease, resection margins, disease recurrence, adequate treatment

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UVOD

Ekstramamarna Pagetova bolest (EMPB) je redak intraepitelni malignitet koji nastaje u oblastima bogatim apokrinim žlezdama, kao što su perineum, vulva, aksila, skrotum i penis [1]. Tačna patogeneza EMPB još uvek nije u potpunosti razjašnjena. Trenutni podaci govore o tome da je EMPB heterogena bolest koja može biti primarna i sekundarna. Primarni EMPB vodi poreklo iz kože, tačnije iz epiderma ili apokrinih znojnih žlezda. Ovaj oblik je u početku ograničen na epitel, ali može da napreduje do invazivnog tumora koji se širi u derm, krvne i limfne sudove, a u uznapredovalom stadijumu može dati limfonodalne ili visceralne metastaze. Sekundarni oblik EMPB je povezan sa širenjem malignih ćelija adenokarcinoma poreklom iz dermalnih adneksalnih žlezdi ili unutar susednog epitela, obično genitourinarnog ili gastrointestinalnog [2]. Incidenca ekstramamarne Pagetove bolesti je 6 na 1 000 000 ljudi godišnje [3], dok penoskrotalna EMPB obuhvata svega 14% svih EMPB [4].

Predstavljamo Vam slučaj osamdeset-jednogodišnjeg muškarca sa penoskrotalnom EMPB.

PRIKAZ SLUČAJA

Muškarac starosti od 81 godine javlja se prvi put 9.2.2023. godine na Institut za onkologiju i radiologiju Srbije (IORS) zbog ulcerisane i eritematozne tumorne promene promera oko 10 cm prekrivene skvamoznim pločama, koja se proteže od preponske regije levo do skrotuma. Tumefakt je eritematozan, prokrvljen i povremeno krvari, a pacijent od tegoba navodi povremeni bol u levoj nozi. Prethodno je učinjena biopsija navedene tumorske promene u drugoj ustanovi, a patohistološki (PH) nalaz je išao u prilog ekstramamarnoj Pagetovoj bolesti. Pacijent je prezentovan konzilijumu IORS-a koji je doneo odluku o operativnom lečenju.

Urađena je ekscizija tumorske promene leve ingvinoskrotalne regije uz primarno zatvaranje defekta. Dobijeni PH nalaz glasi: Imunohistohemijski profil tumorskih ćelija: CK7+, HER2+, CK5/6, HMB45-, p63-. U analiziranom preparatu je prisutan tumor koji po svojim histomorfološkim karakteristikama i imunohistohemijskim osobinama odgovara Pagetovoj bolesti sa invazijom svih slojeva derma, ali ne i potkožnog masnog tkiva, limfovaskularna invazija nije nađena. Bočne ivice resekcije su infiltrisane tumorskim tkivom, dok po dubini nisu infiltrisane, klasifikovan kao pT2.

Pacijent je postoperativno redovno kontrolisan. Nakon 4 meseca se javlja na kontrolni pregled kada su na UZ pregledu ingvinalne regije uočene dve lgl od 11 mm i 8 mm koje su suspektne i otvorene etiologije. Zatim je pacijent upućen na konzilijum koji je doneo odluku da se uradi MSCT.

INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare intraepithelial malignancy that typically occurs in areas rich in apocrine glands, such as the perineum, vulva, axilla, scrotum, and penis [1]. The exact pathogenesis of EMPD is still not completely understood. Current data indicate that EMPD is a heterogenous disease that can be primary and secondary. Primary EMPD originates from the skin, more precisely from the epidermis or apocrine sweat glands. This form is initially limited to the epithelium but can progress to an invasive tumor that spreads to the dermis, as well as blood and lymphatic vessels. In advanced stages, it may lead to lymph node or visceral metastases. The secondary form of EMPD is associated with the spread of malignant adenocarcinoma cells originating from dermal adnexal glands or adjacent epithelium, typically from the genitourinary or gastrointestinal tract [2]. The incidence of extramammary Paget's disease is 6 per 1,000,000 people per year [3], with penoscrotal EMPD accounting for only 14% of all EMPD cases [4].

We present the case of an 81-year-old man with penoscrotal EMPD.

CASE

An 81-year-old man presented to the Institute of Oncology and Radiology of Serbia (IORS) on 9th February 2023 with a first-time complaint of an ulcerated, erythematous tumor measuring approximately 10 cm in diameter, covered with squamous plaques and extending from the left groin to the scrotum. The mass is erythematous and bloody, with occasional bleeding, and the patient reports occasional pain in the left leg. A biopsy of the tumor was previously performed at another institution, with the histopathology results indicating extramammary Paget's disease. The patient was presented to the IORS council, which recommended surgical treatment.

An excision of the tumor in the left inguinoscrotal region was performed, followed by primary closure of the defect. The histopathology report indicates the following immunohistochemical profile of the tumor cells: CK7+, HER2+, CK5/6+, HMB45-, p63-. The analyzed preparation reveals a tumor that, based on its histomorphological and immunohistochemical characteristics, is consistent with Paget's disease. The tumor invades all layers of the dermis but does not extend into the subcutaneous fat tissue, and no lymphovascular invasion was observed. The lateral edges of the resection are infiltrated with tumor tissue, but the infiltration does not extend to the depth, classified as pT2.

The patient was regularly monitored postoperatively. After 4 months, he returned for a follow-up ex-

Na učinjenom MSCT pregledu abdomena i male karlice verifikovane su multiple fokalne promene u jetri po tipu sekundarnih depozita. Retroperitonealno je prisutna limfadenopatija. Uočena je prostata izmenjenog oblika, izrazito nehomogena i neoštre konture, dimenzija 70 x 65 x 61 mm koja se utiskuje u mokraćnu bešiku, ali bez jasno očuvanog masnog plana ka desnoj semenoj vezikuli. Prikazane koštane strukture LS kičme su razređene, sa osteolitičnim, mrljastim i konfluentnim zonama uz izdvajanje korpusa L2 i L3 koji su smanjenog visinskog promera na terenu patološke frakture. Pacijent tada od tegoba navodi bolove u kostima, u desnoj i levoj preponi, kao i slabost donjih ekstremiteta 3 nedelje unazad.

Pacijent je ponovo prikazan konzilijumu IORS-a koji je uvidom u nalaz MSCT-a, tegobe koje navodi pacijent, kao i performans status pacijenta (PS3) doneo odluku da se u sklopu kompletne dijagnostičke obrade uradi PSA, CEA, CA19-9, pregled urologa, kolonoskopija, mamografija i MSCT toraksa.

Mamografski nalaz je bio uredan (BIRADS DD2 LD2). Tumorski markeri CEA 435,38 ng/mL; CA19-9 59 U/mL; PSA 4,41 ng/mL. Na učinjenom MSCT pregledu toraksa opisuje se jedan subpleuralni nodus u plućima spreda medijastinalno do 7 mm – sekundarni depozit granuloma i savetovano je dalje praćenje. Zbog teškog opšteg stanja pacijenta (PS4) pregled urologa i kolonoskopija nisu učinjeni.

Na Slikama 1-5 vidi se histološki presek tumora sa ekstramamarnom Pagetovom bolešću.

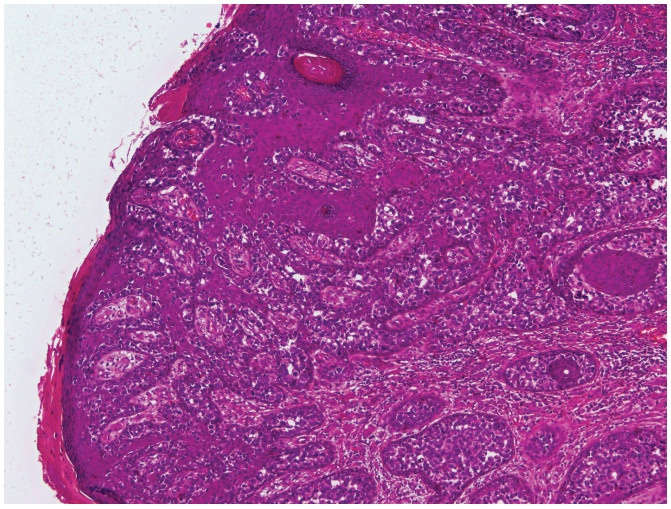
Pacijent je potom, ponovo prikazan konzilijumu, koji imajući u vidu opšte stanje pacijenta i raširenost bolesti, donosi odluku da specifično onkološko leče-

amination, during which an ultrasound of the inguinal region revealed two suspicious lesions, measuring 11 mm and 8 mm, with an indeterminate etiology. The patient was then referred to the council, which decided to proceed with a multidetector computed tomography (MDCT) scan.

The MDCT examination of the abdomen and pelvis revealed multiple focal lesions in the liver, consistent with secondary deposits. Lymphadenopathy was present retroperitoneally. An irregularly shaped prostate with extremely heterogeneous and indistinct contours, measuring 70 x 65 x 61 mm, was observed. It was compressing the urinary bladder and lacked a clearly defined fat plane adjacent to the right seminal vesicle. The bony structures of the lumbar spine showed rarefaction with osteolytic, patchy, and confluent areas. The L2 and L3 vertebral bodies were notably affected, exhibiting reduced height in the region of a pathological fracture. At that time, the patient reported bone pain in both the right and left groin, along with weakness in the lower extremities, which had persisted for 3 weeks.

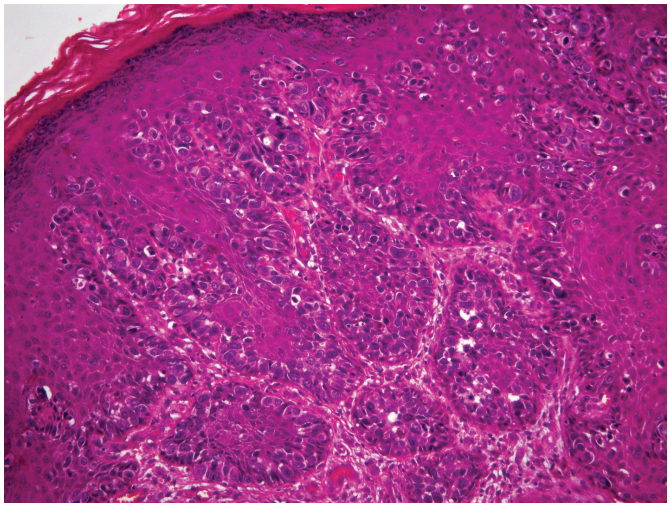
The patient was presented again to the IORS council, which, after reviewing the MDCT findings, the patient's reported symptoms, and his performance status (PS3), decided to conduct a comprehensive diagnostic work-up. This included PSA, CEA, and CA19-9 tests, a urological examination, colonoscopy, mammography, and MDCT of the thorax.

The mammographic findings were normal (BI-RADS DD2 LD2). CEA tumor markers were as follows: CEA 435.38 ng/mL; CA19-9 59 U/mL; PSA 4.41 ng/mL. The MDCT examination of the thorax identified



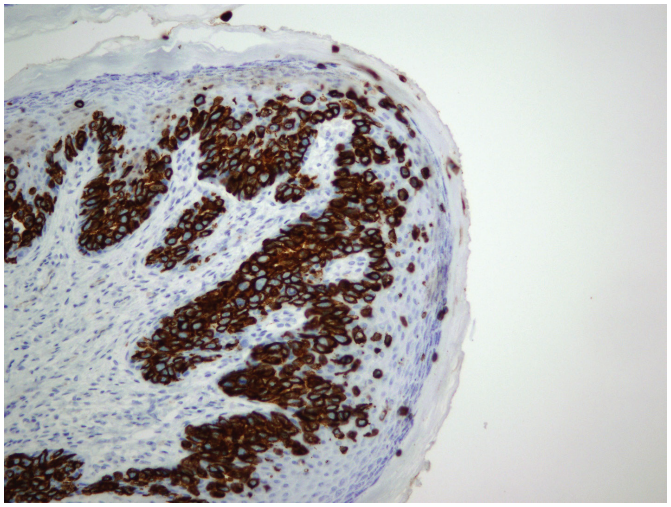
Slika 1. Ekstramamarna Pedžetova bolest. Neoplastične ćelije obilne citoplazme raspoređene u konfluentna gnezda i kao pojedinačne ćelije koje se šire kroz epiderm. (H&E, 10x)

Picture 1. Extramammary Paget's disease. Neoplastic cells with abundant cytoplasm are arranged in confluent nests and as single cells throughout the epidermis (H&E, 10x).



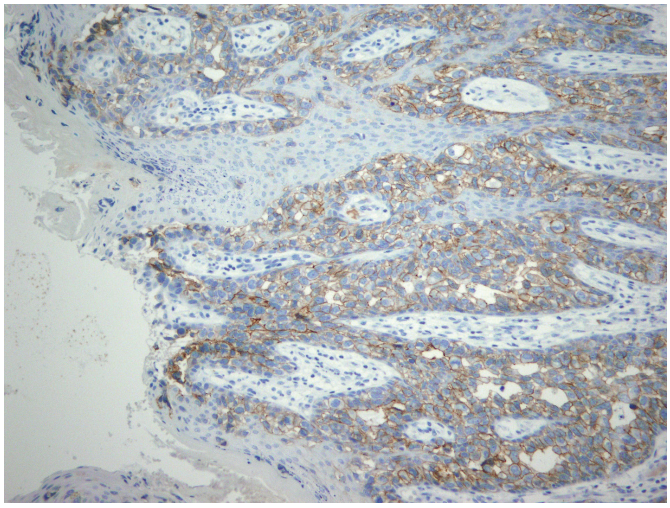
Slika 2. Ekstramamarna Pedžetova bolest. Klasteri i pojedinačne Pedžetove ćelije komprimuju bazalne keratinocite uz bazalnu membranu. (H&E, 20x)

Picture 2. Extramammary Paget's disease. The clusters and single Paget cells compress the basal keratinocytes against the basement membrane (H&E, 20x).



Slika 3. Ekstramamarna Pedžetova bolest. Neoplastične ćelije pokazuju citoplazmatsku i membransku pozitivnost na CK7. (CK7, 20x)

Picture 3. Extramammary Paget's disease. Neoplastic cells show cytoplasmic and membranous CK7 staining (CK7, 20x).



Slika 4. Ekstramamarna Pedžetova bolest. Neoplastične ćelije pokazuju umerenu membransku pozitivnost na HER2. (HER2 , 20x)

Picture 4. Extramammary Paget's disease. Neoplastic cells show moderate, complete membranous staining for HER2 (HER 2 , 20x).

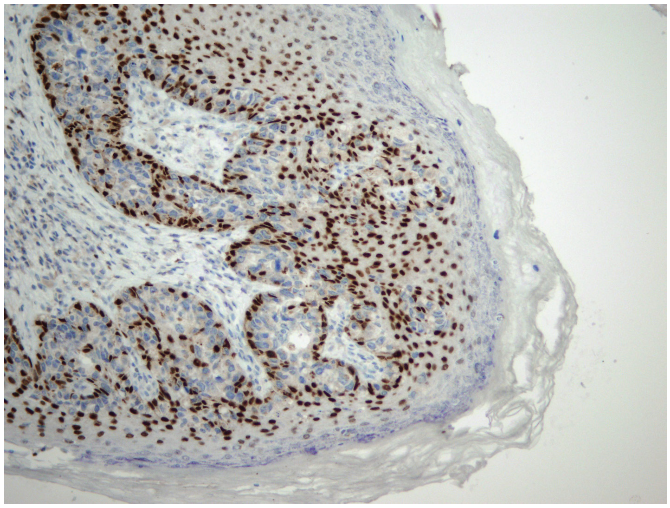
nje nije indikovano i da je u nastavku lečenja potrebno sprovoditi simptomatsku i suportivnu terapiju.

Pacijent je zbog bolova u kostima, levoj i desnoj preponi, kao i slabosti donjih esktremiteta pregledan u ambulanti za bol IORS-a gde je propisana simptomatska terapija: 1. Durogesic flaster 25 ugr/h, 2. Oramorph sirup 0,2%, 3. Fresubin 2 kcal, 4. Fortecortin tbl 4 mg, 5. Laktuloza sirup, 6. Klometol tbl.

DISKUSIJA

Sa istorijskog gledišta, Kroker je prvi opisao EMPB skrotuma i penisa 1889. godine [5]. Klinička manifestacija ove bolesti je kao nespecifični dobro ograničeni eritematozni, zadebljali ili beli ljuskavi plak nepravilnih granica [6,7]. EMPB moramo razlikovati od drugih oboljenja skvamoznog karcinoma, melanoma i benignih papuloskvamoznih bolesti. Penoskrotalne lezije se mogu javiti u preponama, a zatim se mogu proširiti na skrotum i penis. Lezije su najčešće praćene svrabom, ali se mogu javiti i peckanje i otok. Ingvinalna limfadenopatija može biti dijagnostikovana u nekim slučajevima i biti povezana sa edemom nogu [8].

Kao što je i u uvodu rečeno, EMPB je redak entitet, čija incidenca iznosi svega 6 / 1 000 000 osoba [3]. Vulva predstavlja najčešće mesto bolesti, kod oko 65% ukupno obolelih [9]. Za razliku od EMPB vulve, penoskrotalna EMPB se javlja znatno ređe. U Sjedinjenim Američkim Državama u periodu od 1973. do 2002. godine opisano je svega 100 slučajeva [10]. Makroskopski lezije izgledaju kao jasno ograničeni eritematozni plakovi, koji svrbe, mogu da ulcerišu i krvare. S obzirom na kliničku sliku često se pogrešno dijagnostikuje kao ekcem, lihen sklerozus, kontaktni dermatitis, seboroič-



Slika 5. Ekstramamarna Pedžetova bolest. Neoplastične ćelije su negativne na p63, dok ćelije epiderma pokazuju jedarnu imunopozitivnost na p63. (p63,20x)

Picture 5. Extramammary Paget's disease. Neoplastic cells are negative for p63, whereas epidermal cells show nuclear p63 positivity (p63, 20x).

a subpleural nodule in the lung, measuring up to 7 mm, located from the mediastinal region. This finding, which could represent a secondary deposit or granuloma, warranted further follow-up. Due to the patient's severe general condition (PS4), the urological examination and colonoscopy were not conducted.

Figures 1-5 display histological sections of a tumor diagnosed with extramammary Paget's disease.

The patient was reviewed by the council again, which, considering the patient's overall condition and disease progression, concluded that specific oncological treatment was not indicated. Instead, they recom-

ni dermatits, gljivična infekcija ili, najčešće, psorijaza, što često dovodi do odlaganja postavljanja prave dijagnoze, upućivanja pogrešnom specijalisti i pogrešne terapije [4,11]. Ukoliko lezije u regijama koje su bogate apokrinim žlezdama ne daju odgovor na prethodno ordiniranu terapiju, uvek u obzir treba uzeti EMPB [12].

U studiji naučnika sa Univerziteta Džon Hopkins u Baltimoru prosečna starost pacijenata sa penoskrotalnom EMPB je iznosila 73 godine (63-87) [13].

Da bi se postavila dijagnoza EMPB neophodan je patohistološki pregled biopsiranog materijala. Dijagnoza se potvrđuje prisustvom Pagetovih ćelija na rutinskom hematoksilin-eozin bojenju. Većina slučajeva EMPB predstavlja primarni adenokarcinom koji verovatno potiče od pluripotentnih ćelija iz bazalnog sloja epidermisa. Za razliku od primarne EMPB, sekundarna EMPB je povezana sa drugim anatomski bliskim malignitetima. Najveći broj malignitета koji je povezan sa EMPB penisa i skrotuma jesu maligniteti genitourinarnog trakta (prostate i mokraćne bešike), kao i rektalni karcinom [14].

Prognoza lokalne EMPB je znatno bolja od invazivne, zato se i terapije razlikuju. U slučaju neinvazivne EMPB, terapija obuhvata nekoliko modaliteta lečenja: hiruršku resekciju, radioterapiju, topikalnu hemioterapiju, i fototerapiju. Najbolji vid terapije za neinvazivnu EMPB je svakako široka ekscizija lezije, a najveći broj autora preporučuje margine od 1 - 3cm u zdravo tkivo. S obzirom da se EMPB širi i van makroskopski uočljivih granica preporučuje se Mohsova mikrografska hirurgija koja ima niži stepen lokalnog recidiva bolesti (33% vs 23%). Disekcija pripadajućih limfnih nodusa je neophodna u slučaju njihovog zahvatanja. Profilaktička disekcija limfnih nodusa se ne preporučuje i nema nikakav benefit.

Kod pacijenata sa invazivnom EMPB hirurgija ne predstavlja kurativni tretman, pa je često adjuvantna hemio- i radioterapija neophodna. Citotoksični agensi 5-fluorouracil i Mitomicin C su efekasni kod neadekvatno ekscidiranih i uznapredovalih EMPB [15].

U studiji azijske grupe autora koja je obuhvatila ukupno 95 pacijenata lečenih od EMPB u periodu od 1993. do 2020. godine, petogodišnje preživljavanje pacijenata je iznosilo 79,3%, dok je ukupno desetogodišnje preživljavanje iznosilo 64,7%. Pacijenti sa sekundarnim oblikom EMPB, s obzirom na pridruženi drugi malignitet, su imali značajno kraće preživljavanje [16].

ZAKLJUČAK

Ekstramamarna Pegetova bolest predstavlja retku bolest koja zahvata kožu koja je bogata apokrinim žlezdama u regijama vulve, skrotuma, penisa i aksila. Pošto se bolest nalazi i izvan klinički vidljivih lezija pozitivne ivice resekcije su česte, a to predstavlja glavni faktor rizika za recidiv bolesti. Trenutno je terapija izbora šimended continuing with symptomatic and supportive therapy.

Due to bone pain, pain in the left and right groin, and weakness in the lower extremities, the patient was evaluated at the IORS pain clinic. Symptomatic therapy was prescribed, including: 1. Durogesic patch 25 μg/h, 2. Oramorph syrup 0.2%, 3. Fresubin 2 kcal, 4. Fortecortin tablets 4 mg, 5. Lactulose syrup, and 6. Clometol tablets.

DISCUSSION

From a historical point of view, Crocker was the first to describe EMPD of the scrotum and penis in 1889 [5]. The clinical manifestation of this disease typically presents as a non-specific, well-demarcated erythematous plaque that may be thickened or covered with white, scaly patches, often with irregular borders [6,7]. EMPD must be differentiated from other conditions, including squamous cell carcinoma, melanoma, and benign papulosquamous diseases. Penoscrotal lesions may initially develop in the groin and subsequently spread to the scrotum and penis. Lesions are most often accompanied by itching, but burning and swelling may also occur. In some cases, inguinal lymphadenopathy may be diagnosed, which can be associated with leg edema [8].

As mentioned in the introduction, EMPD is a rare condition with an incidence of only 6 per 1,000,000 people [3]. The vulva is the most common site for the disease, affecting approximately 65% of patients [9]. Compared to vulvar EMPD, penoscrotal EMPD occurs much less frequently. In the period between 1973 and 2002, only 100 cases were presented in the United States of America [10]. Macroscopically, the lesions present as well-circumscribed erythematous plaques that may itch, ulcerate, and bleed. Due to its clinical presentation, the condition is often misdiagnosed as eczema, lichen sclerosus, contact dermatitis, seborrheic dermatitis, fungal infection, or, most commonly, psoriasis. This frequent misdiagnosis can result in delays in reaching the correct diagnosis, referrals to inappropriate specialists, and incorrect treatments [4,11]. If lesions in areas rich in apocrine glands do not respond to the previously prescribed therapy, EMPD should always be considered [12].

In a study conducted by scientists from Johns Hopkins University in Baltimore, the average age of patients with penoscrotal EMPD was 73 years, ranging from 63 to 87 [13].

A diagnosis of EMPD requires a histopathological examination of the biopsied tissue. The diagnosis is confirmed by the presence of Paget's cells on routine hematoxylin-eosin staining. Most cases of EMPD are

roka lokalna ekscizija lezije ili Mohsova mikrografska hirurgija. Raritet ovog entiteta čini istraživanja koja za cilj imaju lečenje ove bolesti izuzetno teškim. Potrebne su znatno veće studije koje bi nam dale dalje smernice kako pristupiti pacijentima sa EMPB.

Sukob interesa: Nije prijavljen.

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primary adenocarcinomas that probably originate from pluripotent cells in the basal layer of the epidermis. Unlike primary EMPB, secondary EMPB is associated with other anatomically close malignancies. The majority of malignancies associated with EMPD of the penis and scrotum are linked to genitourinary tract cancers, particularly prostate and bladder cancer, as well as rectal cancer [14].

The prognosis for localized EMPD is significantly better than for invasive disease, which is why the treatment approaches differ. For noninvasive EMPD, treatment options include surgical resection, radiotherapy, topical chemotherapy, and phototherapy. The most effective treatment for non-invasive EMPD is wide excision of the lesion, with most experts recommending margins of 1-3 cm in healthy tissue. Since EMPD often extends beyond macroscopically visible boundaries, Mohs micrographic surgery is recommended, as it offers a lower rate of local disease recurrence (23% vs 33%). Dissection of the associated lymph nodes is required if they are involved. Prophylactic lymph node dissection is not recommended, as it has no benefit.

In patients with invasive IMPB, surgery is not a curative treatment, so adjuvant chemotherapy and radiotherapy are often necessary. Cytotoxic agents such as 5-fluorouracil and Mitomycin C are effective for treating inadequately excised and advanced EMPD [15].

In a study conducted by an Asian research group involving 95 patients treated for EMPD between 1993 and 2020, the five-year survival rate was 79.3%, and the ten-year survival rate was 64.7%. Patients with secondary EMPD, due to the presence of an associated second malignancy, had a significantly shorter survival [16].

CONCLUSION

Extramammary Paget's disease is a rare condition that affects skin areas rich in apocrine glands, including the vulva, scrotum, penis, and axilla. Because the disease often extends beyond clinically visible lesions, positive resection margins are common, which is a major risk factor for disease recurrence. Currently, the preferred therapies are wide local excision of the lesion or Mohs micrographic surgery. The rarity of this condition makes research focused on developing effective treatments particularly challenging. Larger studies are needed to provide more guidance on how to approach and treat patients with EMPD.

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