CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

An immunocompetent young patient with tuberculosis of the penis: a challenging case

MARIA ROTARU[1)], SORINA TĂBAN[2)], MONA ŢĂROI[3)], VIRGIL PĂTRAŞCU[4)], FLORINA-LIGIA POPA[5)]

[1)]*Department of Dermatology, "Victor Papilian" Faculty of Medicine, "Lucian Blaga" University of Sibiu, Romania*
[2)]*Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timisoara, Romania*
[3)]*Department of Dermatology, Emergency County Hospital, Sibiu, Romania*
[4)]*Department of Dermatology, University of Medicine and Pharmacy of Craiova, Romania*
[5)]*Department of Rehabilitation Medicine, "Victor Papilian" Faculty of Medicine, "Lucian Blaga" University of Sibiu, Romania*

Abstract

Tuberculous chancre is an extremely rare form of cutaneous tuberculosis. The genital area is a possible site of presentation. We present a case of a young male with a persistent balanopreputial ulceration resembling a luetic chancre with negative serology for syphilis. The diagnosis was based on the specific pathologic features and the positive intradermal reaction to tuberculin. A successful treatment was achieved by combining antituberculosis treatment and surgical approach with circumcision. After six months of antituberculosis treatment, the patient developed paradoxical inguinal lymph node enlargement, which, after surgical excision and biopsy, was not followed by a relapse of the disease and needed no further therapy. Tuberculosis should be considered a potential diagnosis in the case of a persistent genital ulcer.

Keywords: mucocutaneous tuberculosis, genital chancre, granuloma, penile ulcer, primary inoculation.

Introduction

Skin tuberculosis, with its many clinical forms, represents only 1–2% of the newly diagnosed cases of Koch bacillus infection [1]. Usually, the etiologic agent is *Mycobacterium tuberculosis*, but, exceptionally, it can be *M. bovis* or Calmette–Guérin bacillus [2]. Most commonly, skin tuberculosis is of endogenous origin, produced by blood or lymph dissemination or by direct extension from a latent or active infection [3]. In extremely rare cases, in individuals who have not previously contacted the disease, skin tuberculosis is produced by primary exogenous inoculation on injured skin, thus creating the clinical picture of tuberculosis (TB) chancre [4]. There are many other diseases characterized by penile ulcer, and the most frequent is syphilis.

In the present paper, we report an unusual case with giant penian chancre, initially suspected as being primary syphilis, but after several negative syphilis serology tests, a positive intradermal reaction to tuberculin and specific histopathological findings, it was later confirmed as a tuberculous chancre.

Case report

A 17-year-old immunocompetent male has been admitted in the Department of Dermatology in May 2013, presenting a persistent and painful balanopreputial ulceration, which had occurred six weeks priorly. The current disease began as a group of three papular lesions localized on the ventral area of the penis, which gradually ulcerated and fused to form a unique large ulceration that destroyed the preputial frenulum. The serology for syphilis including VDRL (venereal disease research laboratory) test and TPHA (*Treponema pallidum* hemagglutination assay) was negative. Based on these data, the disease was originally considered to be a serological negative primary syphilis. The ultramicroscopy and PCR (polymerase chain reaction) for *T. pallidum* were not performed. Lacking any other investigations, the patient had previously been treated in the ambulatory, with Phenoxymethylpenicillinum 3× 1 g/day, for 10 days, and afterwards with Azithromycinum 500 mg/day for another seven days, as a chancroid. Both yielded no positive clinical results, with a rapid increasing in size of the penile ulcer.

Dermatological examination showed a single large, painful and non-indurated ulceration on the ventral area of the penis, about 4/5 cm in diameter, with sharply demarcated irregular margins, and yellowish grey deposits on the base (Figure 1).

Multiple painless mobile lymph node enlargements were found on both sides of the inguinal region, with the largest coming up to less than 1 cm in diameter. No other associate diseases or symptoms were detected during the general examination.

Syphilis serology (VDRL and TPHA) tests came back negative on repeated occasions. Laboratory findings that included a complete blood count and liver and kidney function tests were normal. The HIV (human immunodeficiency virus) serological test was also negative. Ulceration swabs were positive for *Escherichia coli* and *Staphylococcus aureus*, both sensitive to Ciprofloxacin on drug susceptibility testing (DST). The chest X-ray film revealed no pathological changes.

Due to the presence of infection identified by a bacteriologic exam and to the rapid increase of the ulceration size, a systemic treatment with Ciprofloxacin 1 g/day for 10 days, combined with local disinfectant, was initiated. This did not trigger any improvements. Because

the clinical aspect showed no improvement after the administration of a systemic broad-spectrum antibiotics and topical treatment, the patient was transferred in the Department of Urology for a complete excision of the ulceration, by circumcision, after obtaining the patient's informal consent. Because the entire ulcerated preputial skin was resected, a rotated flap plasty was done, over the urethra and then the skin was sutured. After two days, the dressing was removed and the patient was discharged from the hospital with a clean postoperative wound. The one-week reevaluation showed healed surgical sutures. Six months after the surgical intervention, the clinical aspect showed a complete healing of the lesion (Figure 2).

Figure 1 – ***Macroscopic aspect with large, non-indurated, giant ulceration of the ventral area of the penis.***

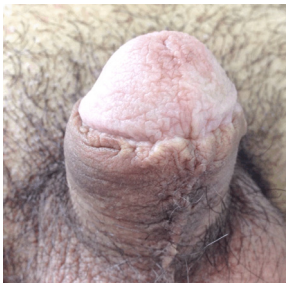

Figure 2 – ***Clinical aspect, with locally healed, six months after surgical excision.***

The pathological examination of the skin specimen showed extensive areas of epidermal ulceration, with a presence of granulomatous lesions, partially fused, which were formed of epitheloid cells, Langhans giant cells and lymphocytes at the periphery. In the centre of the granulomas, there were areas of granular, eosinophilic necrosis and in other areas, of fibrinoid necrosis (Figures 3 and 4). The lower dermis there is a rich inflammatory infiltrate, consisting of lymphocytes and plasma cells surrounding the small vessels, with plump endothelial cells (Figure 5). This pathological aspect was highly suggestive of tuberculous granulomas (Figure 3). Based on clinical evolution and the histopathological results, the diagnosis of tuberculoid chancre of the penis was established.

The patient was referred to the Department of Pneumology for further investigation and specific treatment. The skin test with 2 IU of tuberculin showed a 17 mm erythema and III Palmer induration. The mycobacterial urine culture was negative. Antituberculosis therapy (ATT) was initiated using a HRZE (Isoniazid 2×150 mg, Rifampicin 2×300 mg, Pyrazinamide 4×500 mg and Ethambutol 4×400 mg) daily drug regimen for two months, followed by a regimen of HR (Isoniazid 2×150 mg, Rifampicin 2×300 mg) three times weekly, for four months. An epidemiological investigation was also conducted, but revealed no source of infection, neither in the patient nor the patient's sexual partner.

After six months of antituberculosis treatment, the patient returned to our Department, presenting an inguinal lymph node enlargement on the right side. No local erythema, pain or other symptoms were present. A clinical examination of this area showed a unilateral growth of lymph nodes, with multiple visibly enlarged, firm and mobile nodes of maximum 2 cm in size compared to the previous examination. He was again referred to the Department of Urology for surgical excision and a biopsy of the lymph node. Before sending the lymph nodes for histopathological examination, swabs were taken from the pathological content of the excised lymph nodes for a direct microscopic examination and bacterial and mycobacterial culture on the Löwenstein medium. The microscopic examination of the acid-fast bacilli smear was negative, and the cultures revealed no growth. The histopathological exam from the lymph node showed focal replacement of follicular architecture through confluent giant epithelioid granulomas with central caseating necrosis. All sections stained with the specific histochemical techniques (PAS, Giemsa, Grocott, Ziehl–Nielsen) have not isolated bacilli, fungi and parasites. The granulomatous lesions with a confluence of tuberculous follicles and caseous necrosis (Figures 6 and 7) were very suggestive of tuberculous lymphadenitis.

The Grocott (Figure 8) and Ziehl–Neelsen (Figure 9) stainings highlighted the caseous necrosis in granulomatous lesions of the lymph node.

The Goldner–Szekely (GS) trichromic staining showed the presence of some extended hemorrhagic and necrosis foci, diffusely disseminated in the cavernous body structure, outside or inside the tuberculous granulomas (Figure 10). These extended hemorrhagic areas are due to the structure alteration of blood vessels in the cavernous bodies by the tuberculous infection.

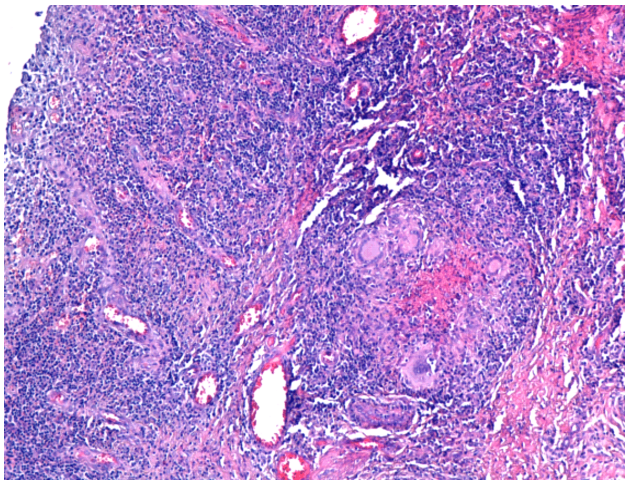

Figure 3 – ***Necrotizing granulomas in the dermis; ulceration of the epidermis. HE staining, ×100.***

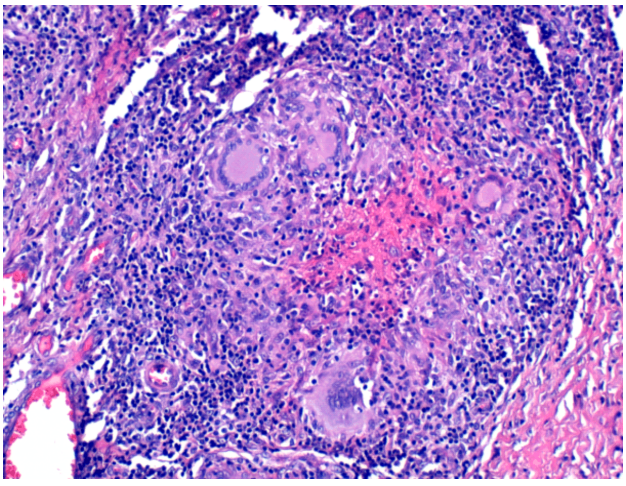

Figure 4 – ***Confluent necrotizing granulomas in dermis, detail of the previous figure. HE staining, ×200.***

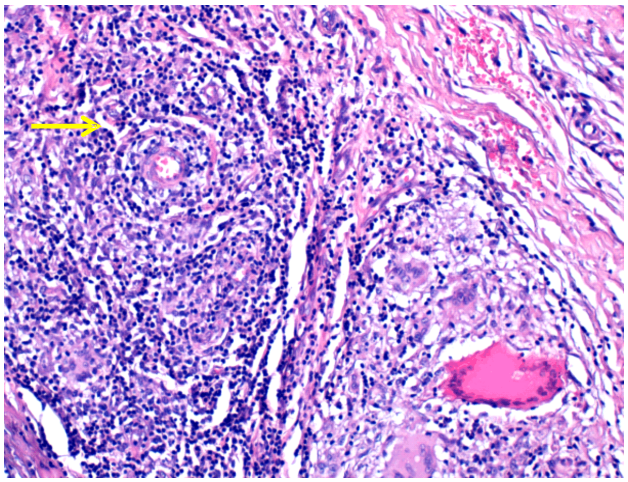

Figure 5 – ***Granulomas made up of Langhans giant cells and epithelioid cells. Aspects of vasculitis (arrow). HE staining, ×400.***

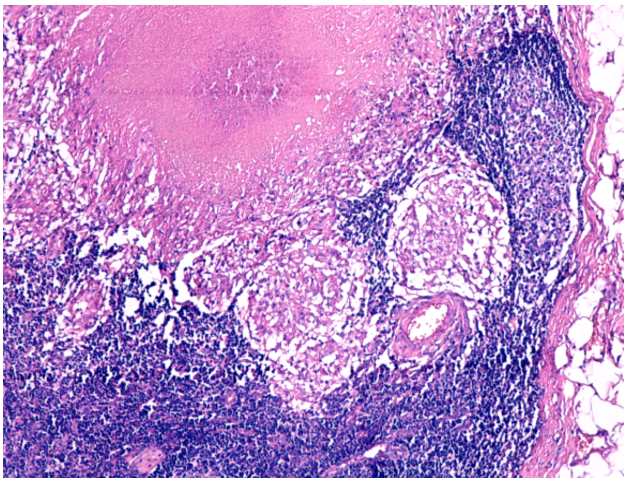

Figure 6 – ***Caseous necrosis and granulomatous lesions in lymph node. HE staining, ×100.***

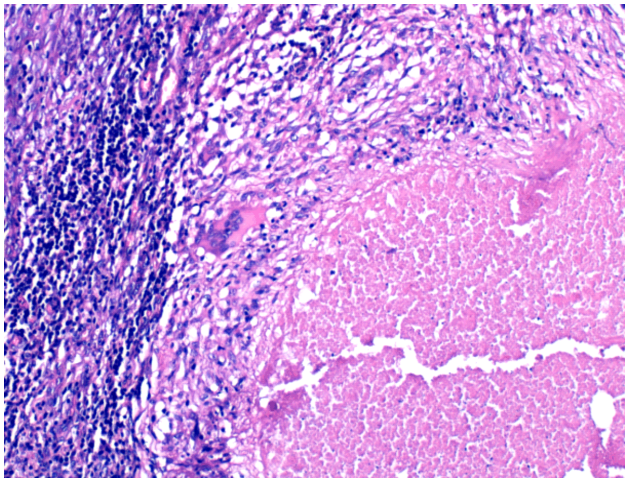

Figure 7 – ***Detail of the previous figure. HE staining, ×400.***

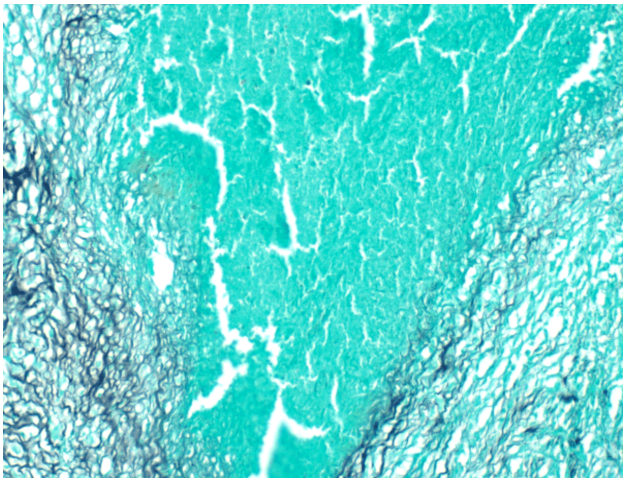

Figure 8 – ***Caseous necrosis in lymph node. Grocott staining, ×200.***

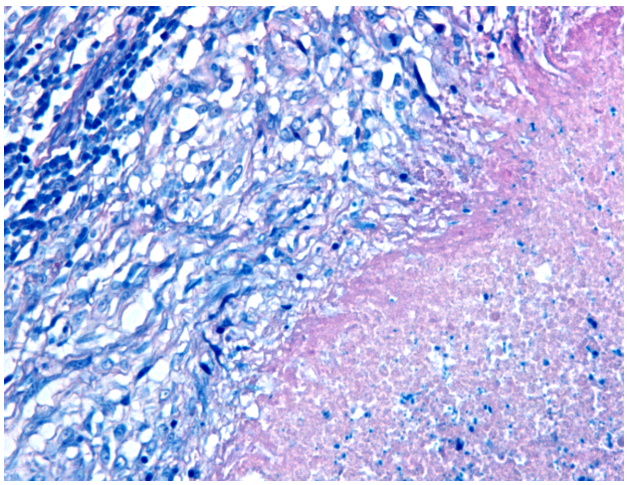

Figure 9 – ***Lymph node with necrotizing granulomatous lesion, negative for Mycobacterium tuberculosis. Ziehl–Neelsen staining, ×400.***

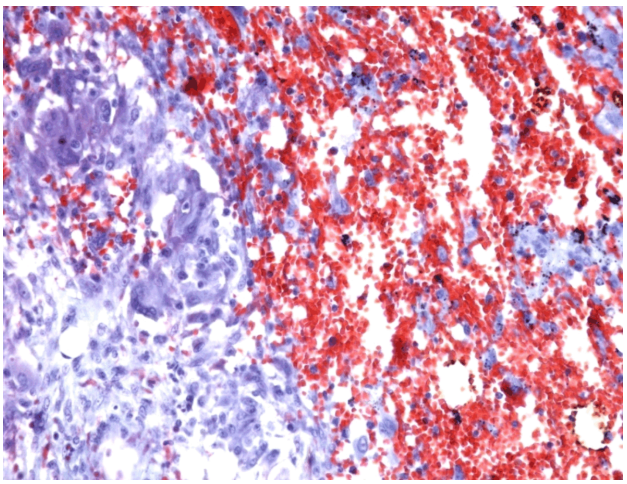

Figure 10 – ***Extended areas of hemorrhage and necrosis, diffusely disseminated in the structure of cavernous bodies. GS trichromic staining, ×200.***

For the positive and differential diagnosis, from the histological material included in paraffin, there were performed serial sections in the microtome, placed on poly-L-Lysine blades and prepared for immunohistochemistry studies. Thus, there was identified the presence and distribution of macrophages, using the CD68 antibody (Clone KP1, 1/200, Dako), of T-lymphocytes by using the CD3 antibody (Clone F7.2.38, 1/100 Dako) and of B-lymphocytes by using the CD20 antibody (Clone L26, 1/100, Dako).

Of the three types of inflammatory cells, the most numerous were the macrophages. They were highlighted both in the tuberculous nodules and in the necrosis and hemorrhage areas (Figure 11). Intensely positive to CD68 were also the multinuclear giant cells (the Langhans cells) (Figure 12), as well as the epithelioid cells demarcating the tuberculous granulomas.

The T-lymphocytes appeared disseminated in the entire tuberculous granuloma structure (Figure 13), and also in the surrounding areas, while the B-lymphocytes were identified at the granuloma periphery, being almost absent from its structure (Figure 14).

The paradoxical reaction, like the growth of the lymph nodes with a fistulizing tendency after six months of administering a specific antituberculosis treatment, is explained by the latent evolution of peripheral adenopathy in tuberculosis, knowing that the initiation of the specific therapy does not stop the evolution of the already affected lymph nodes – it only stops the spreading of the infection to the other groups. For this reason, the pulmonologist concluded that the patient did not need a reinitiation of the ATT (anti-tuberculosis therapy), taking into account that the smear and the culture on Löwenstein medium from the excised lymph node were negative, with the exclusion of the relapse of the disease. In the reevaluation period up until present day, the patient's general state has been very good.

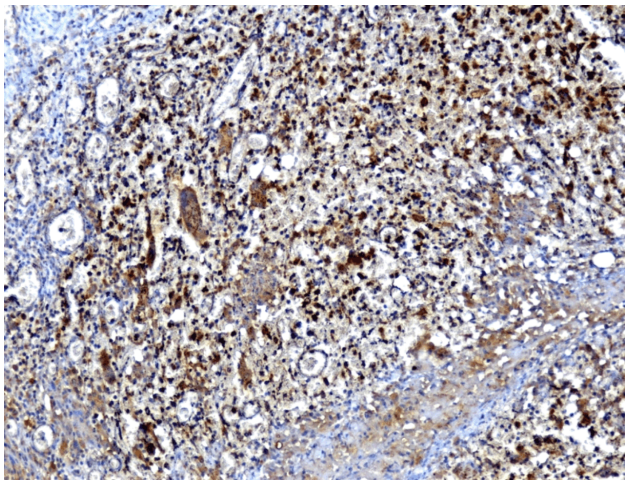

Figure 11 – ***Overall microscopic image of a tuberculous nodule in the cavernous bodies, where we may observe an intense reaction to the CD68 antibody, showing the presence of a high number of macrophage cells. Anti-CD68 antibody immunomarking, ×100.***

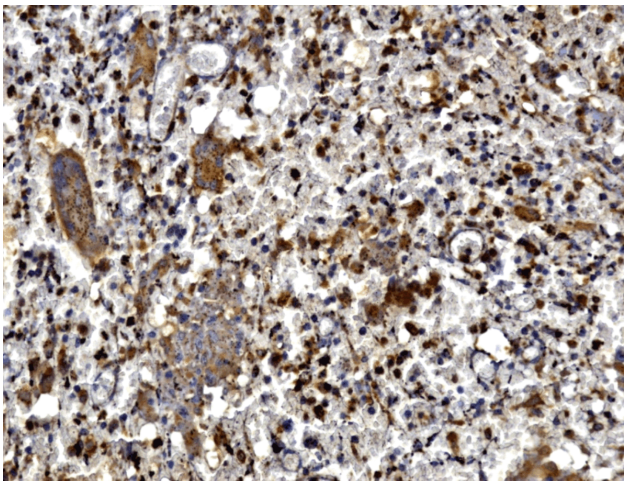

Figure 12 – ***Multinuclear giant cells (Langhans cells), with an intensely positive cytoplasmic reaction to CD68 antibody (detail from the previous image). Anti-CD68 antibody immunostaining, ×200.***

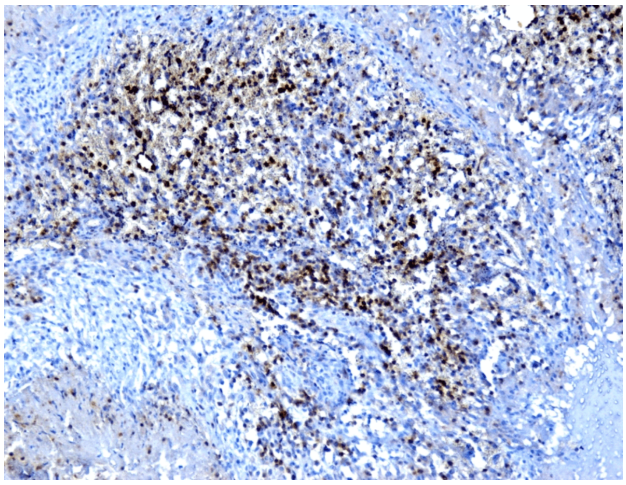

Figure 13 – ***T-lymphocytes relatively homogeneously disseminated in the tuberculous granuloma structure. Anti-CD3 antibody immunostaining, ×100.***

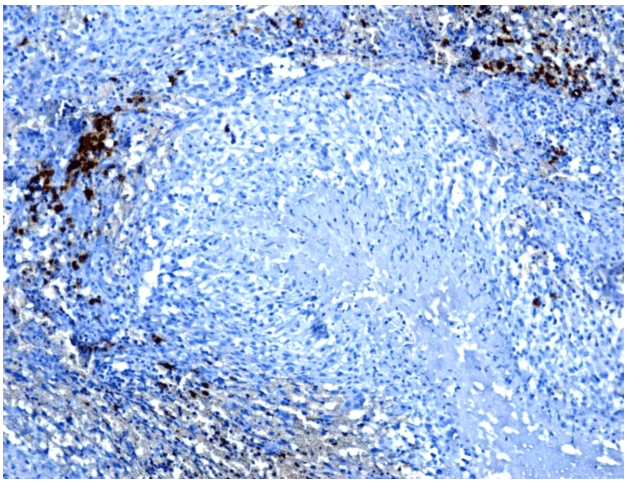

Figure 14 – ***B-lymphocytes arranged in a "crown" at tuberculous granuloma periphery. Anti-CD20 antibody immunostaining, ×100.***

Discussion

Common sites for primary inoculation of tuberculosis are the face and other exposed cutaneous areas after ritual circumcision, tattooing, ear piercing, etc. [5, 6]. Acute primary gingivitis can occur after ingestion of contaminated milk with *M. bovis*. Lewis found 89 cases of primary penile tuberculosis in 1949. Of them, 74 cases were a result of circumcision, 12 of coitus, two of oral sex, one of wearing infected clothing [7–9]. Since 1992, several cases of tuberculous balanitis and penile ulcers have been described as rare complications of an intravesical instillation of BCG (bacillus Calmette–Guérin) [10].

In our case, the transmission pathway remains unclear, but oral sex with an infected non-declared, BK (bacillus

Koch) positive partner could be possible. In the patient's declared sexual partner, the chest X-ray did not show any pathological findings, the IDR (intradermal reaction) to PPD (purified protein derivative) was negative, the gynecological exam was normal and negative urine of Löwenstein cultures. In this situation, other possible ways of transmission could be oral sex with an undeclared partner with active lung tuberculosis or wearing infected clothes [11, 12].

Presented with this clinical picture of penile ulceration, we had to rule out several conditions. Firstly, syphilitic chancre, characterized as a firm painless ulceration, sharply demarcated with spontaneous healing in 4–6 weeks was ruled out [13]; in some cases of syphilitic chancre, the infection with other bacterial agents could explain the rapid evolution, but this requires syphilis serology to be positive and the histopathological aspect specific to vasculitis and inflammatory infiltrate rich in lymphocytes and plasma cells. Chancroid has a painful, fibrin-covered ulceration with undetermined and non-indurated borders associating fixed suppurative adenopathy. In lymphogranuloma venerum, self-limited genital ulcers, followed by painful inguinal lymphadenopathy, appear; genital herpes is usually recurrent, with a short evolution (days) of painful erythematous recurrent vesicular lesions that sometimes ulcerate. Another possible disease was pyoderma gangrenosum, characterized by a rapidly growing ulceration with undermined violaceous margins. In carcinoma of the penis, the ulceration is long lasting, indurated, and more often affects elderly patients. Most of these conditions have clinical and serological characteristic features, which were not seen in our situation.

The histopathological aspect of granulomas with necrosis can be found in many granulomatous disorders, such as Wegener granulomatosis (granulomas with necrosis, infarction), Churg–Strauss granulomatosis (granulomas, necrosis) or sarcoidosis (granulomas without necrosis). Among these, only tuberculosis developed granulomas with caseous necrosis [14].

A paradoxical reaction after an effective anti-tuberculous treatment is a well-known phenomenon described since 1955, and is defined as the clinical or radiological worsening of pre-existing lesions or development of new lesions, without relapse of the disease, in a patient whose condition had initially improved with tuberculostatic therapy. In such cases, ruling out drug resistance, poor compliance or secondary infection is crucial [15]. In our case, the negative acid-fast bacilli smear and negative culture from the lymph nodes confirmed that there was no need for another anti-tuberculous treatment scheme.

On the other hand, the superinfection of the specific ulceration with *Escherichia coli* and *Staphylococcus* in our case could have been a factor to negatively influence the local aspects and evolution of the TB chancre.

Among case particularities, we count: young age; the penial localization of the lesion; negative HIV serology; the absence of an immunocompromised status; the association of tuberculous adenopathy with the growth of lymph nodes in the first six months of anti-tuberculous treatment and the paradoxical reaction following effective therapy. The diagnosis of tuberculous adenopathy was made with the help of a histopathological exam of the lymph node. In spite of the anamnestic and laboratory information, we could not establish the transmission pathway in our case. Cutaneous tuberculosis is one of the differential diagnoses in the case of genital cutaneous ulcerations.

The extrapulmonary tuberculous lesions are quite difficult to be diagnosed clinically [17–19]. There is estimated that extrapulmonary lesions might represent about 15–20% of the total of tuberculous lesions [17]. Tuberculosis localized in the genitourinary tract represents only 2–4% of the total of tuberculous lesions [20]. However, the lesions may affect any structure of the urinary or genital tract. Most often, genital tuberculosis is associated with the presence of other severe conditions, among which the human immunodeficiency virus ranks the first place [21].

In our case, the histopathological and immunohistochemical examinations were essential for the positive and differential diagnosis. The presence of necrosis areas, associated with a high number of epithelioid cells and Langhans cells, allowed the establishment of the positive diagnosis and treatment. The immunohistochemical examinations showed that, in the tuberculous granuloma structure, the main cellular population was represented by macrophages, cells that take various morphological aspects during the local defense reaction. Sometimes, in tuberculosis the histopathological examination as well is difficult to explain, the lesions might be confused with the ones in sarcoidosis, syphilis, syphilis, Crohn's disease, rheumatoid arthritis, etc. [22]. Due to these reasons, we consider that, alongside the clinical and paraclinical examinations, the monitoring the lesion evolution under treatment is essential for a positive diagnosis, especially in the unspecific forms of extrapulmonary tuberculosis.

Conclusions

Among the many clinical forms of cutaneous tuberculosis, we had the chance to meet the rarest one, the tuberculous chancre. In general, a chancre starts out as a papule or a nodule that will eventually ulcerate in two to three weeks to form an irregular, non-healing ulcer with a granulomatous base. Painless regional lymphadenopathy is evident at 3–8 weeks, producing a lympho-cutaneous clinical picture analogous to the Ghon's complex (reaction at the site of inoculation and affected regional lymph nodes). The phenomenon of a paradoxical enlargement of lymph nodes after a treatment is very common among patients with extra-pulmonary tuberculosis or those who are HIV positive. This paradoxical reaction, characterized by lymph node enlargement six months after the administration of effective anti-tuberculous treatment, needed no further therapy, as the negative smear and culture from the excised lymph node has excluded a relapse of the disease.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All the authors had an equal contribution in the study performance.

References

[1] Yasaratne BMGD, Madegedara DM. Tuberculosis of the skin. J Ceylon Coll Phys, 2010, 41(2):83–88.

[2] Frankel A, Penrose C, Emer J. Cutaneous tuberculosis: a practical case report and review for the dermatologist. J Clin Aesthet Dermatol, 2009, 2(10):19–27.

[3] Angus BJ, Yates M, Conlon C, Byren I. Cutaneous tuberculosis of the penis and sexual transmission of tuberculosis confirmed by molecular typing. Clin Infect Dis, 2001, 33(11): e132–e134.

[4] Lee LPY, Chiu WK, Chan HB. Enlarging tuberculous lymph node despite treatment: improving or deteriorating? HK J Paediatr, 2009, 14:42–45.

[5] Reetha AM, Vijayan VK, Prabhakar R. Primary tuberculosis of skin (tuberculous chancre) in an infant of tuberculous mother. Lung India, 1991, 9(4):153–155.

[6] Holt LE. Tuberculosis acquired through ritual circumcision. JAMA, 1913, 61(2):99–102.

[7] Rossi R, Urbano F, Tortoli E, Trotta M, Zuccati G, Cappugi P. Primary tuberculosis of the penis. J Eur Acad Dermatol Venereol, 1999, 12(2):174–176.

[8] Lewis EL. Tuberculosis of the penis; a report of 5 new cases, and a complete review of the literature. J Urol, 1946, 56(6): 737–745.

[9] Konohana A, Noda J, Shoji K, Hanyaku H. Primary tuberculosis of the glans penis. J Am Acad Dermatol, 1992, 26(6): 1002–1003.

[10] Sharma VK, Sethy PK, Dogra PN, Urvashi S, Das P. Primary tuberculosis of glans penis after intravesical Bacillus Calmette Guerin immunotherapy. Indian J Dermatol Venereol Leprol, 2011, 77(1):47–50.

[11] Pal DK, Kundu AK, Chakraborty S, Das S. Tuberculosis of penis: report of two cases. Indian J Tub, 1996, 43(4):203–204.

[12] Narayana AS, Kelly DG, Duff FA. Tuberculosis of the penis. Br J Urol, 1976, 48(4):274.

[13] Semon HCG. Tuberculosis and syphilis. Br J Vener Dis, 1939, 15(3):159–170.

[14] James DG. A clinicopathological classification of granulomatous disorders. Postgrad Med J, 2000, 76(898):457–465.

[15] Gupta PR. Difficulties in managing lymph node tuberculosis. Lung India, 2004, 21(4):50–53.

[16] Bravo FG, Gotuzzo E. Cutaneous tuberculosis. Clin Dermatol, 2007, 25(2):173–180.

[17] Purohit M, Mustafa T. Laboratory diagnosis of extra-pulmonary tuberculosis (EPTB) in resource-constrained setting: state of the art, challenges and the need. J Clin Diagn Res, 2015, 9(4):EE01–EE06.

[18] Popescu MR, Călin G, Strâmbu I, Olaru M, Bălăşoiu M, Huplea V, Zdrancotă C, Pleşea RM, Enache SD, Pleşea IE. Lymph node tuberculosis – an attempt of clinico-morphological study and review of the literature. Rom J Morphol Embryol, 2014, 55(2 Suppl):553–567.

[19] Petrescu IO, Gheonea C, Voican CS, Ciobanu D, Niţu M, Petrescu F. Disseminated tuberculosis presenting as febrile seizures with fatal evolution in an infant. Rom J Morphol Embryol, 2014, 55(4):1483–1489.

[20] Wolf JS Jr, McAninch JW. Tuberculous epididymo-orchitis: diagnosis by fine needle aspiration. J Urol, 1991, 145(4):836–838.

[21] Dell'Atti L. Unusual isolated tuberculous epididymitis. Case report. G Chir, 2014, 35(5–6):134–136.

[22] Shrivastava G, Bajpai T, Bhatambare GS, Patel KB. Genital tuberculosis: comparative study of the diagnostic modalities. J Hum Reprod Sci, 2014, 7(1):30–33.

Corresponding author

Sorina Tăban, Associate Professor, MD, PhD, Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, 2 Efitimie Murgu Square, 300041 Timişoara, Romania; Phone +40748–331 269, e-mail: sorinataban@yahoo.com

Received: January 12, 2015

Accepted: June 9, 2015