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HPV AND BUSCHKE-LOWENSTEIN DISEASE

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ABSTRACT:
INTRODUCTION. HUMAN PAPILLOMAVIRUS (HPV) IS A VIRAL INFECTION WHICH GENERATES EPITHELIAL TUMOURS OF THE MUCOUS MEMBRANES AND SKIN ESPECIALLY WARTS. THE DIMENSIONS OF THE WARTS COULD VARY AMONG INDIVIDUALS FROM A FEW MILLIMETRES TO A CONSIDERABLE SIZE BEING CALLED GIANT CONDYLOMA ACUMINATUM (GCA). THIS GIANT CONDYLOMA ACUMINATUM WAS FIRST DESCRIBED BY BUSCHKE AND LÖWENSTEIN IN 1925 ON PENILE FORESKIN, NOWADAYS KNOWN AS BUSCHKE – LOWENSTEIN TUMOUR (BLT).
MATERIAL AND METHODS. THE PURPOSE OF THIS PAPER IS TO REVIEW THE AVAILABLE DATA REGARDING THE ETIOPATHOGENY OF BLT DIAGNOSIS AND NEW LINES OF TREATMENT. WE USED PUBMED AND SCOPUS DATABASES FOR REVIEWS AND FULL ARTICLES.
CONCLUSIONS. BUSCHKE – LOWENSTEIN IS A RARE DISEASE CAUSED BY INFECTION WITH HPV, ESPECIALLY ASSOCIATED WITH "SEMI – MALIGNANT " VERRUCOUS CARCINOMA OR SQUAMOUS CELL CARCINOMA. COINFECTION WITH HIV ENHANCE THE ONCOGENIC ABILITY OF HPV, BUT THE ONCOGENIC PROCESS IS SLOW, SO AN EARLY REMOVAL OF THE LESION WHEN NOTICED BY THE PATIENT IS USEFUL TO PREVENT A GCA. PRE-EXPOSURE AND POST-EXPOSURE VACCINES ARE VERY IMPORTANT IN PREVENTING BLT AND REDUCING THE VIRAL LOAD IN THE INFECTED.

Keywords: HPV, BUSCHKE-LOWENSTEIN, RARE DISEASE.

INTRODUCTION

Human papillomavirus (HPV) is a viral infection which generates epithelial tumors of the mucous membranes and skin. HPV is a nonenveloped, icosahedral virus, with a genome coresponding to all HPVs of approximately 8-kilobase pair molecule of circular, double stranded DNA[10]. In Romania, the main cancer screening measure is HPV vaccination, supported by the Public Health Ministry, but unfortunately parents are still reluctant to vaccinate their young girls[11]. The actual classification system for HPV is based on resemblance in genomic sequences and usually associated with the three major clinical categories:

- Anogenital or mucosal.
- Epidermodysplasiaverruciformis.
- Nongenital cutaneous.

The anogenital warts are a painless outgrowth on the skin surface, in most cases associated with human papillomavirus (HPV) infection subtypes 6 and 11[12]. Almost 80% of genital warts are usually correlated with low-risk HPV subtypes 6 and 11 but the high-risk HPV subtypes 16, 18, 52, and 56 are also implicated, coinfection occurring frequently, causing important morbidity in

[10] Berceanu, C; Paitici, S; Berceanu, S; Bratila, E; et al. *Colposcopic, histologic and immunohistochemical assessment in cervical intraepithelial lesions.* Rev Chim (Bucharest), 2018; 69(8): 2245-50
[11] Stanculescu, R; Bratila, E; Bausic, V; Vladescu, T. *The triage of low-grade cytological abnormalities by the immunocytological expression of cyclin-dependent kinase inhibitor p16INK4a versus human papillomavirus test: a real possibility to predict cervical intraepithelial neoplasia CIN2 or CIN2+*. Rom J Morphol Embryol, 2013; 54(4):1061-5
[12] Papapanagiotou, IK; Migklis, K; Ioannidou, G; et al. *Giant condyloma acuminatum -malignant transformation.* Clin Case Rep., 2017; 5: 537

general population[13]. The Pap smear is a trustful screening test even during pregnancy, with abnormalities in 5-8% of the results[14]. Generally, the majority of warts are benign andregress after 18 months, but the dynamics between the virus and the immunologic response of the host can transform a long-standing wart in a malignant one[15]. The dimensions of the warts could vary among individuals, from a few millimetres to a considerable size, being called giant condylomataacuminatum (GCA). The giant condyloma acuminatum was first described by Buschke and Löwenstein in 1925 on penile foreskin[16]. GCA is rare, having a 0.1% incidence rate in general population, but on the other hand it has almost 50% recurrence rate[17]. There are also environment factors that increase the risk of GCA like: sex (male), smokers, beginningof sexual life at young age, poor hygiene, uncircumcised men.

ETIOPATHOGENY

Different therories are present in the literature regarding the malignant potential of this disease. One of them states that this is a disease with high risk of evolving in agressive squamous cell carcinoma (SCC). Georgi Tchernev et al concluded that the period of malignant transformation ranges between 3 to 5 years. After malignant transformation, it usually turns into more aggressive disease, which frequently metastasizes to the pelvic organs and regional lymph nodes. This category of patients has generally a bad prognosis in comparison with the patients that treat the disease in the early stages[18].

The second theory about this disease consider it a 'semi-malignant' verrucous carcinoma, due to their invasive local evolution[19]. Some authors describe Buschke-Lowenstein tumors (BLT) as a variant of verrucous carcinoma, while others authors consider it as a differentdisease[20]. Chu et

[13] McCutcheon, T. *Anal condyloma acuminatum*. Gastroenterol Nurs., 2009; 32: 342; Mehedintu, C; Bratila, E; Cirstoiu, M; Vladareanu, R; Antonovici, MR; Brinduse, LA; Berceanu, C; Gherghiceanu, F; Navolan, D; Ionescu, OM; Criveanu, M. *A fixed herbal combination-A new approach in HPV cervical infection treatment*. Farmacia, 2018, 66(3): 502-506; Mehedintu, C; Plotogea, M; Antonovici, M; Todea, C. *The human papillomavirus infection*. Dermato Venerol, 2013;58:277-86.

[14] Berceanu, C; Bratila, E; Cirstoiu, M; et al. *Colposcopic assessment and management of HPV infection in pregnancy*. Ginecologia. 2016;14(4):6-12

[15] Gormley, RH; Kovarik, CL. *Human papillomavirus-related genital disease in the immunocompromised host: part I*. J Am AcadDermatol., 2012, 66: 867; Steinbach, A; Riemer, AB. *Immune evasion mechanisms of human papillomavirus: an update*. Int J Cancer, 2018; 142: 224.

[16] Spinu, D; Radulescu, A; Bratu, O; Checherita, IA; Ranetti, AE; Mischianu, D. *Giant condyloma acuminatum - Buschke-Lowenstein disease - a literature review.* Chirurgia, 2014, 109(4): 445-450.

[17] Badiu, DC; Manea, CA; Mandu, M; Chiperi, V; Marin, IE; Mehedintu, C; Popa, CC; David, OI; Bratila, E; Grigorean, VT. *Giant Perineal Condyloma Acuminatum (Buschke-Lowenstein Tumour): A Case Report*. Chirurgia (Bucharest), 1990, 111(5):435-438

[18] Wells, M; Robertson, S; Lewis, F.. *Squamous carcinoma arising in giant perianal condyloma associated with human papilloma virus 6 and 11*. Histopathology, 1988, 12: 319; Handisurya, A; et al. *Rapid progression of an anal Buschke-Lowenstein tumour into a metastasising squamous cell carcinoma in an HIV-infected patient.* Eur. J. Dermatol., 2008, 19: 329.

[19] Schwartz, RA. *Verrucous carcinoma of the skin and mucosa*. J Am Acad Dermatol., 1995; 32: 1; Virgilio, E; Balducci, G; Mercantini, P; et al. *Perianal giant condylomaacuminatum of Buschke-Loewenstein: a carcinoma-like condyloma or a condyloma-like carcinoma?* ANZ J Surg., 2015; 85: 394.

[20] Chu, QD; Vezeridis, MP; Libbey, NP; Wanebo, HI. *Giant condyloma acuminatum (Buschke-Lowenstein tumor) of the anorectal and perianal regions: analysis of 42 cases.* Dis Colon Rectum., 1994; 37: 950; Ahsaini, M; Tahiri, Y;

al evaluated almost 40 cases of BLT in the literature and reviewed their management and behaviour. The tumour was reported to have a significant rate of recurrence and a risk of malignant transformation to squamous cell carcinoma (SCC), with no distant metastases. Trombetta et al noticed the presence of neoplastic foci in as many as 50% of the 52 reports of patients undergoing surgery for BLT[21].

Also, studies showed that the early stages of Buschke-Löwenstein tumours and genital warts have similar histopathological and clinical features. In advanced stages of BLT, ithas a specific clinical feature like: uneven surface, cauliflower like shape, white to yellowish colour. From the histopathologicalpoint of view, the tumour is characterized by: papillomatous formations, with acanthosis and hyperplastic epithelium, consisting in cells with hyperchromatic nuclei and pale cytoplasm, maintaining the basal membrane. In the literature, studies concluded that HPV 16 and 18 are frequently connected with thetransformation of the tumour to squamous cell carcinoma, while HPV 6 and 11 most often transform inverrucouscarcinoma[22]. Also, the routine methods of investigation, such as PCR or immunohistochemistry testing for HPV, are justifiedand very important for morphological confirmation of Buschke-Löwenstein tumours and especially for choosing the correct treatment option of these patients. These investigation methodsare of key importancefor starting the exact treatment for the less favorable, poorly differentiated variants of squamous cell carcinoma with potential for lymph node metastases.

PATHOLOGY

Sexually transmitted infection with HPV is characterized by the invasion the genital epidermal basal layer cells as a consequence of micro-abrasions. Human Papilloma Virus finalize its cycle outside the genital epithelial basement membrane, and the E7 gene of HPV decrease the capacity of the antigen presenting cells in the skin, facilitating the virus to stay hidden for extended periods of time sothe virusavoid the host immune response.In conclusion, E6 and E7 oncogenes damage the host cells to induce telomerase resulting in cellular immortalization of the infected cellsandcause chronic oxidative stress increasing the susceptibility of damaging the DNA and starting the way for carcinogenesis[23]. Studies concluded that coinfection with HIV/HSV-1 boost the oncogenesis and the patient positive for HSV-1 IgG beingvulnerable for carcinomatous transition[24]. Squamous cell clusters with keratinization among the condyloma stroma and increased mitotic activity in histopathological examination indicates nests of carcinomatous transformation. SCC of the anogenital area is a slow growing tumor, but associated with hypercalcemia suggests an aggressive phenotypic change and a poor prognosis.

Tazi, MF; et al. *Verrucous carcinoma arising in an extended giant condyloma acuminatum (Buschke-Löwenstein tumor): a case report and review of the literature*. J Med Case Rep., 2013; 7: 273.

[21] Trombetta, LJ; Place, RJ. *Giant condyloma acuminatum of the anorectum: trends in epidemiology and management: report of a case and review of the literature*. Dis Colon Rectum., 2001; 44:1878.

[22] Tchernev, G. *Sexually transmitted papillomavirus infections: epidemiology pathogenesis, clinic, morphology, important differential diagnostic aspects, current diagnostic and treatment options*. An. Bras. Dermatol., 2009; 84: 377.

[23] Katzenellenbogen, R. *Telomerase induction in HPV infection and oncogenesis*. Viruses., 2017; 9:180.

[24] Hara, Y; Kimoto, T; Okuno, Y; Minekawa, Y. *Effect of herpes simplex virus on the DNA of human papillomavirus 18*. J Med Virol., 1997; 53: 4; Dimitriadis, GK; Angelousi, A; Weickert, MO; Randeva, HS; Kaltsas, G; Grossman, A. *Paraneoplastic endocrine syndromes*. Endocr Relat Cancer. 2017; 24: 173.

TREATMENT

The first choice of treatment for giant Buschke – Löwensteintumour is considered wide excision of the lesion. Surgery alone has good results - a disease-free status in 45% of patients[25]. The treatmentoption is influenced by several factors, including the size and thickness of the lesions, anatomic location of the lesions, quantity, HPV classification, immune-competentor immune-compromisedstatus but, no current treatment acquires complete HPV eradication[26].

More than that, oral and topical chemotherapy is used with success as adjuvants to surgery or as treatment for recurrences. Exemple of topical therapy alone, such as 5-fluorouracil or Interferon (IFN), are not sufficient to prevent progression or control the disease[27].

Topical cidofovir is also used as gel 1.5%, with results even in cases with no response to conventional treatment. A case reported in literature noted that bleomycin injected intralesional in the wound was effective, with visible results and with no recurrence at 2 years after treatment[28].

The theory that postulated the viral origin of these tumors made IFN a chimiotherapy agent for this etiology. A reported case of genital CGA argues that IFN 2-alfa can induce the apparent complete resolution after 6 months of treatment[29]. Intralesional administration was effective, with complete responses in 47-62% of cases. Recurrence is frequent, with a rate of 40%. Large lesions represent an indication for systemic administration of IFN.

An infiltrating condylomaacuminatum with giant dimensionssuffered a major response after 9 months of continuous treatment with IFN administration twice weekly, although changes in dimensions were not observed in the first several months.

Imiquimod, a topically-applied aminoquinoline that is an immune modulator that induces interferon production,was considerdeffective in combination with carbon dioxide laser ablation in unstable patients, who were unable to tolerate surgery, whose tumor was positive for HPV-6[30].

There are some reported cases that described the use of traditional systemic antitumor agents, such as bleomycin, cisplatin, leucovorin and methotrexate for patients with recurrence disease after multiple surgeries for CGA[31]. There were no evidences of active disese 1 year later. Use of mitomycin-C and 5-fluorouracil determined a tumor shrinkage in combination with

[25] Renzi, A; Giordano, P; Renzi, G; Landolfi, V; Del Genio, A; Weiss, EG. *Buschke-Lowenstein tumor successful treatment by surgical excision alone: a case report*. Surg Innov., 2006, 13: 69.
[26] Fathi, R; Tsoukas, MM. *Genital warts and other HPV infections: established and novel therapies*. Clin Dermatol., 2014, 32: 299.
[27] Ambriz-González, G; Escobedo-Zavala, LC; Carrillo de la Mora, F; et al. *Buschke-Löwenstein tumor in childhood: a case report*. J Pediatr Surg., 2005, 40,: 25-27.
[28] Badiu, DC; Manea, CA; Mandu, M; Chiperi, V; Marin, IE; Mehedintu, C; Popa, CC; David, OI; Bratila, E; Grigorean, VT. *Giant Perineal Condyloma Acuminatum (Buschke-Lowenstein Tumour): A Case Report*. Chirurgia (Bucharest), 1990, 111(5):435-438; Toro, JR; Sanchez, S; Turiansky, G; Blauvelt, A. *Topical cidofovir for the treatment of dermatologic conditions: verruca, condyloma, intraepithelial neoplasia, herpes simplex and its potential use in smallpox*. Dermatol Clin., 2003, 21: 301.
[29] Geusau, A; Heinz-Peer, G; Volc-Platzer, B; Stingl, G; Kirnbauer, R. *Regression of deeply infiltrating giant condyloma (Buschke-Löwenstein tumor) following long-term intralesional interferon alfa therapy*. *Arch Dermatol*., 2000, 136: 707.
[30] Heinzerling, LM; Kempf, W; Kamarashev, J; Hafner, J; Nestle, FO. *Treatment of verrucous carcinoma with imiquimod and CO2 laser ablation*. *Dermatology*., 2003, 207: 119
[31] Ilkay, AK; Chodak, GW; Vogelzang, NJ; Gerber, GS. *Buschke-Lowenstein tumor: therapeutic options including systemic chemotherapy*. *Urology*., 1993, 42: 599

radiotherapy. For vaginal CGA, use of Etretinat, a synthetic oral retinoid and photodynamic therapy represented a success.

Radiation therapy remains a controversial method of treatment. Few studies presented evidence of an aggressive behavior after radiation therapy, but more than a few cases in literature document resolution of small tumors after this type of therapy[32]. In some cases, of a patient with poor surgical risk, if it is necessary, a large dose of radiation minimizes the chances of mutation and may be effective. As an example, the literature describes a case ofa patient who remained disease-free when he was reevaluated at 20 months after therapy with radiation at 4500 cGy in 25 fractions[33].

Bulky tumors which have exophytic growth and tumor size more than 10 cm in their greatest diameter, have been shrunk with more types of therapy; preoperative hemoradiation, radical surgery[34], sometimes followed by reconstructive surgery, when necessary[35].

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[32] Butler, TW; Gefter, J; Kleto, D; Shuck, EH 3rd; Ruffner, BW. *Squamous-cell carcinoma of the anus in condylomaacuminatum. Successful treatment with preoperative chemotherapy and radiation*. *Dis Colon Rectum*., 1987, 30: 293

[33] Sobrado, CW; Mester, M; Nadalin, W; Nahas, SC; Bocchini, SF; Habr-Gama, A. *Radiation-induced total regression of a highly recurrent giant perianal condyloma: report of case. Dis Colon Rectum.*, 2000, 43: 257.

[34] Spinu, D; Bratu, O; Marcu, D; Mischianu, D; Huica, R; Surcel, M; Munteanu, A; Socea, B; Bodean, O; Ursaciuc, C. *The use of ELISA and PCR in identifying correlations between viral infections and benign prostatic hypertrophy*. Rev Chim (Bucharest), 2018, 69(3): 645-649; Socea, LI; Visan, DC; Barbuceanu, SF; Apostol, TV; Bratu, OG; Socea, B. *The antioxidant activity of some acylhydrazones with dibenzo[a,d][7]annulene moiety*. Rev Chim (Bucharest), 2018, 69(4): 795-797; Tiglis, M; Neagu, TP; Elfara, M; Diaconu, CC; Bratu, OG; Vacaroiu, IA; Grintescu, IM. *Nefopam and its role in modulating acute and chronic pain*, Rev Chim (Bucharest), 2018, 69(10): 2877-2880; Spinu, D; Bratu, O; Popescu, R; Marcu, D; Radulescu, A; Mischianu, D. *Clostridium difficile-an emerging plague*. Romanian Journal of Military Medicine, 2015, 118(3): 12-15; Radulescu, A; Madan, V; Aungurenci, A; Bratu, O; Farcas, C; Dinu, M; Mischianu, D. *Antibiotic resistant urinary tract infections in an urology ward*. Romanian Journal of Military Medicine, 2015, 118(3): 20-22; Mischianu, D; Florescu, I; Madan, V; Iatagan, C; Bratu, O; Oporan, A; Giuglea, C. *Peno-scrotal limphedema with giant hydrocele-surgical treatment particularities*. Journal of Medicine and Life, 2009, 2(1): 72-75; Spinu, D; Radulescu, A; Iatagan, C; Popescu, R; Madan, V; Bratu, O; Ranetti, AE; Mischianu, D. *Bilateral inguinoscrotal Buschke-Lowenstein disease-a case report*. Revista Română de Urologie, 2013, 12(1): 41-43; Spinu, D; Mischianu, D; Bratu, O; Aungurenci, A; Manache, S; Ciuca, A. *HPV implications in benign prostatic impairments-a literature review*. Modern Medicine, 2014, 21(4): 298-303.

[35] Spinu, D; Bratu, O; Aungurenci, A; Marcu, D; Ursaciuc, C; Isvoranu, G; Peride, I; Niculae, A; Mischianu, D. *Epstein Barr Virus and Cytomegalovirus in prostate-a controversial subject*. Modern Medicine, 2015, 22(3): 259-263; Spinu, D; Bratu, O; Oprea, I; Marcu, D; Mischianu, D. *Human papilloma virus infection in men-topographical and procedural aspects-a systematic review*. Revista Română de Urologie, 2016, 15(4): 23-27; Spinu, D; Bratu, O; Marcu, D; Niculae, A; Geavlete, B; Diaconu, C; Mischianu, D. *HPV and bladder cancer-is there a connection?*. Modern Medicine, 2017, 24(1): 1-4; Cozma, CN; Raducu, L; Avino, A; Scaunasu, RV; Bratu, O; Marcu, DR; Jecan, CR. *A rare case of vulvar squamos cell carcinoma; case presentation*. Journal of Clinical and Investigative Surgery, 2018, 3(1): 32-36; Stanescu, AMA; Grajdeanu, IV; Bratu, OG; Iancu, MA; Codreanu, IF; Bejan, GC; Diaconu, CC. *Genetic and therapeutic novelties in atopic dermatitis*. Romanian Journal of Medical Practice, 2018, 13(2): 108-113; Iorga, L; Anghel, R; Manea, M; Marcu, D; Socea, B; Diaconu, C; Bratu, O; Baleanu, V-D; Mischianu, D. *Necrotizing fasciitis of the male genital region – a review of the literature*. Research and Science Today, 2018, suppl 2: 24-36; Manea, M; Marcu, D; Diaconu, C; Socea, B; Dimitriu, M; Baleanu, V-D; Bratu, O. *Thromboprophylaxis in surgical patients*. Research and Science Today, 2018, suppl 2: 57-65; Socea, B; Halau, O; Diaconu, C; Bratu, OG; Neagu, TP; Dimitriu, M; Constantin, VD. *Clostridium difficile infection in surgical patients (literature review)*. Romanian Journal of Medical Practice, 2019, 14(1): 30-33; Constantin, Vlad; Socea, Bogdan; Moculescu, Cezar; Sireţeanu, George; Popa, Florin; *Enteral non-Hodgkinian lymphoma in young age – difficult diagnostic*. Chirurgia, 2009, 104(5): 601-604.

A complete response was obtained after mitomycin C and 5-fluorouracil, administered simultaneously with radiation therapy 50.4 Gy on the tumor bed, and prophylactic radiation of the regional lymph nodes. For recurrent, initial bulky condyloma acuminata, autologous vaccines were prepared with condyloma cells. It was well tolerated and produced a good clinical response.

For all these series, after 1 year, the recurrence rates with various treatments were 50% for surgical excisions alone, 85% for IFN alfa, and 4.6% after excision and vaccination with autologous vaccines[36].

Despite cryotherapy, imiquimod, and surgical debulking, refractory and recurrence disease was successfully treated with combinations of systemic interleukin-2 and topical cidofovir[37].Another treatment combination consists of retinoid administered orally and intramuscular IFN-gamma. The result is a complete clearance in 3 months of a GCA in a 16-year-old girl[38].

CONCLUSIONS

In the literature, there are different theories about the potentiality of Buschke-Löwenstein tumours to be malignant. Sexually transmitted infection with HPV is characterized by the invasion the genital epidermal basal layer cells, as a consequence of micro-abrasions. The HPV oncogenes damage the host cells to induce telomerase, resulting in cellular immortalization of the infected cells, and cause chronic oxidative stress, increasing the susceptibility of damaging the DNA and starting the way for carcinogenesis. The first choice of treatment for giant Buschke - Löwenstein tumour is considered the wide excision of the lesion. Surgery alone have good results - a disease-free status in 45% of patients. The treatment option is influenced by several factors, including the size and thickness of the lesions, anatomic location of the lesions, quantity, HPV classification, immunocompetent or immunocompromised status, but no current treatment acquires complete HPV eradication.

Buschke–Lowenstein tumour is a rare disease caused by infection with HPV, especially associated with ”semi–malignant” verrucous carcinoma or scuamous cell carcinoma. Coinfection with HIV enhances the oncogenic ability of HPV, but the oncogenic process is slow, so an early removal of the lesion when noticed by the patient is useful to prevent a GCA. Pre-exposure and post-exposure vaccines are very important in preventing BLT and reducing the viral load in the infected patients.

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All authors report no potential conflict of interest.

[36] Wiltz, OH; Torregrosa, M; Wiltz, O. *Autogenous vaccine: the best therapy for perianal condyloma acuminata? Dis Colon Rectum*., 1995, 38: 838.
[37] Tian, YP; Yao, L; Malla, P; Song, Y; Li, SS. *Successful treatment of giant condyloma acuminatum with combination retinoid and interferon therapy*. *Int J STD AIDS*., 2012 , 23(6): 445.
[38] Tian, YP; Yao, L; Malla, P; Song, Y; Li, SS. *Successful treatment of giant condyloma acuminatum with combination retinoid and interferon therapy*. *Int J STD AIDS*., 2012 , 23(6): 445

REFERENCES

1. **Berceanu, C; Paitici, S; Berceanu, S; Bratila, E**; et al. *Colposcopic, histologic and immunohistochemical assessment in cervical intraepithelial lesions*. Rev Chim (Bucharest), 2018; 69(8): 2245-50.
2. **Stanculescu, R; Bratila, E; Bausic, V; Vladescu, T**. *The triage of low-grade cytological abnormalities by the immunocytological expression of cyclin-dependent kinase inhibitor p16INK4a versus human papillomavirus test: a real possibility to predict cervical intraepithelial neoplasia CIN2 or CIN2+*. Rom J Morphol Embryol, 2013; 54(4):1061-5.
3. **Papapanagiotou, IK; Migklis, K; Ioannidou, G**; et al. *Giant condyloma acuminatum -malignant transformation*. Clin Case Rep., 2017; 5: 537.
4. **McCutcheon, T**. *Anal condyloma acuminatum*. Gastroenterol Nurs., 2009; 32: 342.
5. **Mehedintu, C; Bratila, E; Cirstoiu, M; Vladareanu, R; Antonovici, MR; Brinduse, LA; Berceanu, C; Gherghiceanu, F; Navolan, D; Ionescu, OM; Criveanu, M**. *A fixed herbal combination-A new approach in HPV cervical infection treatment*. Farmacia, 2018, 66(3): 502-506.
6. **Mehedintu, C; Plotogea, M; Antonovici, M; Todea, C**. *The human papillomavirus infection*. Dermato Venerol, 2013;58:277-86.
7. **Berceanu, C; Bratila, E; Cirstoiu, M**; et al. *Colposcopic assessment and management of HPV infection in pregnancy*. Ginecologia. 2016;14(4):6-12.
8. **Gormley, RH; Kovarik, CL**. *Human papillomavirus-related genital disease in the immunocompromised host: part I*. J Am AcadDermatol., 2012, 66: 867.
9. **Steinbach, A; Riemer, AB**. *Immune evasion mechanisms of human papillomavirus: an update*. Int J Cancer, 2018; 142: 224.
10. **Spinu, D; Radulescu, A; Bratu, O; Checherita, IA; Ranetti, AE; Mischianu, D**. *Giant condyloma acuminatum - Buschke-Lowenstein disease - a literature review.* Chirurgia, 2014, 109(4): 445-450.
11. **Badiu, DC; Manea, CA; Mandu, M; Chiperi, V; Marin, IE; Mehedintu, C; Popa, CC; David, OI; Bratila, E; Grigorean, VT**. *Giant Perineal Condyloma Acuminatum (Buschke-Lowenstein Tumour): A Case Report*. Chirurgia (Bucharest), 1990, 111(5):435-438.
12. **Wells, M; Robertson, S; Lewis, F.**. *Squamous carcinoma arising in giant perianal condyloma associated with human papilloma virus 6 and 11*. Histopathology, 1988, 12: 319
13. **Handisurya, A**; et al. *Rapid progression of an anal Buschke-Lowenstein tumour into a metastasising squamous cell carcinoma in an HIV-infected patient.* Eur. J. Dermatol., 2008, 19: 329.
14. **Schwartz, RA**. *Verrucous carcinoma of the skin and mucosa*. J Am Acad Dermatol., 1995; 32: 1.
15. **Virgilio, E; Balducci, G; Mercantini, P**; et al. *Perianal giant condylomaacuminatum of Buschke-Loewenstein: a carcinoma-like condyloma or a condyloma-like carcinoma?* ANZ J Surg., 2015; 85: 394.
16. **Chu, QD; Vezeridis, MP; Libbey, NP; Wanebo, HI**. *Giant condyloma acuminatum (Buschke-Lowenstein tumor) of the anorectal and perianal regions: analysis of 42 cases*. Dis Colon Rectum., 1994; 37: 950.
17. **Ahsaini, M; Tahiri, Y; Tazi, MF**; et al. *Verrucous carcinoma arising in an extended giant condyloma acuminatum (Buschke-Löwenstein tumor): a case report and review of the literature*. J Med Case Rep., 2013; 7: 273.
18. **Trombetta, LJ; Place, RJ**. *Giant condyloma acuminatum of the anorectum: trends in epidemiology and management: report of a case and review of the literature*. Dis Colon Rectum., 2001; 44:1878.
19. **Tchernev, G**. *Sexually transmitted papillomavirus infections: epidemiology pathogenesis, clinic, morphology, important differential diagnostic aspects, current diagnostic and treatment options*. An. Bras. Dermatol., 2009; 84: 377.
20. **Katzenellenbogen, R**. *Telomerase induction in HPV infection and oncogenesis*. Viruses., 2017; 9:180.
21. **Hara, Y; Kimoto, T; Okuno, Y; Minekawa, Y**. *Effect of herpes simplex virus on the DNA of human papillomavirus 18*. J Med Virol., 1997; 53: 4.
22. **Dimitriadis, GK; Angelousi, A; Weickert, MO; Randeva, HS; Kaltsas, G; Grossman, A**. *Paraneoplastic endocrine syndromes*. Endocr Relat Cancer. 2017; 24: 173.
23. **Renzi, A; Giordano, P; Renzi, G; Landolfi, V; Del Genio, A; Weiss, EG**. *Buschke-Lowenstein tumor successful treatment by surgical excision alone: a case report*. Surg Innov., 2006, 13: 69.

24. **Fathi, R; Tsoukas, MM**. *Genital warts and other HPV infections: established and novel therapies*. Clin Dermatol., 2014, 32: 299.
25. **Ambriz-González, G; Escobedo-Zavala, LC; Carrillo de la Mora, F**; et al. *Buschke-Löwenstein tumor in childhood: a case report*. J Pediatr Surg., 2005, 40,: 25-27.
26. **Toro, JR; Sanchez, S; Turiansky, G; Blauvelt, A**. *Topical cidofovir for the treatment of dermatologic conditions: verruca, condyloma, intraepithelial neoplasia, herpes simplex and its potential use in smallpox*. Dermatol Clin., 2003, 21: 301.
27. **Geusau, A; Heinz-Peer, G; Volc-Platzer, B; Stingl, G; Kirnbauer, R**. *Regression of deeply infiltrating giant condyloma (Buschke-Löwenstein tumor) following long-term intralesional interferon alfa therapy*. *Arch Dermatol*., 2000, 136: 707.
28. **Heinzerling, LM; Kempf, W; Kamarashev, J; Hafner, J; Nestle, FO**. *Treatment of verrucous carcinoma with imiquimod and CO2 laser ablation*. *Dermatology*., 2003, 207: 119.
29. **Ilkay, AK; Chodak, GW; Vogelzang, NJ; Gerber, GS**. *Buschke-Lowenstein tumor: therapeutic options including systemic chemotherapy*. *Urology*., 1993, 42: 599.
30. **Butler, TW; Gefter, J; Kleto, D; Shuck, EH 3rd; Ruffner, BW**. *Squamous-cell carcinoma of the anus in condylomaacuminatum. Successful treatment with preoperative chemotherapy and radiation*. *Dis Colon Rectum*., 1987, 30: 293.
31. **Sobrado, CW; Mester, M; Nadalin, W; Nahas, SC; Bocchini, SF; Habr-Gama, A**. *Radiation-induced total regression of a highly recurrent giant perianal condyloma: report of case*. *Dis Colon Rectum*., 2000, 43: 257.
32. **Spinu, D; Bratu, O; Marcu, D; Mischianu, D; Huica, R; Surcel, M; Munteanu, A; Socea, B; Bodean, O; Ursaciuc, C**. *The use of ELISA and PCR in identifying correlations between viral infections and benign prostatic hypertrophy*. Rev Chim (Bucharest), 2018, 69(3): 645-649.
33. **Socea, LI; Visan, DC; Barbuceanu, SF; Apostol, TV; Bratu, OG; Socea, B**. *The antioxidant activity of some acylhydrazones with dibenzo[a,d][7]annulene moiety*. Rev Chim (Bucharest), 2018, 69(4): 795-797.
34. **Tiglis, M; Neagu, TP; Elfara, M; Diaconu, CC; Bratu, OG; Vacaroiu, IA; Grintescu, IM**. *Nefopam and its role in modulating acute and chronic pain*, Rev Chim (Bucharest), 2018, 69(10): 2877-2880.
35. **Spinu, D; Bratu, O; Popescu, R; Marcu, D; Radulescu, A; Mischianu, D**. *Clostridium difficile-an emerging plague*. Romanian Journal of Military Medicine, 2015, 118(3): 12-15.
36. **Radulescu, A; Madan, V; Aungurenci, A; Bratu, O; Farcas, C; Dinu, M; Mischianu, D**. *Antibiotic resistant urinary tract infections in an urology ward*. Romanian Journal of Military Medicine, 2015, 118(3): 20-22.
37. **Mischianu, D; Florescu, I; Madan, V; Iatagan, C; Bratu, O; Oporan, A; Giuglea, C**. *Peno-scrotal limphedema with giant hydrocele-surgical treatment particularities*. Journal of Medicine and Life, 2009, 2(1): 72-75.
38. **Spinu, D; Radulescu, A; Iatagan, C; Popescu, R; Madan, V; Bratu, O; Ranetti, AE; Mischianu, D**. *Bilateral inguinoscrotal Buschke-Lowenstein disease-a case report*. Revista Română de Urologie, 2013, 12(1): 41-43.
39. **Spinu, D; Mischianu, D; Bratu, O; Aungurenci, A; Manache, S; Ciuca, A**. *HPV implications in benign prostatic impairments-a literature review*. Modern Medicine, 2014, 21(4): 298-303.
40. **Spinu, D; Bratu, O; Aungurenci, A; Marcu, D; Ursaciuc, C; Isvoranu, G; Peride, I; Niculae, A; Mischianu, D**. *Epstein Barr Virus and Cytomegalovirus in prostate-a controversial subject*. Modern Medicine, 2015, 22(3): 259-263.
41. **Spinu, D; Bratu, O; Oprea, I; Marcu, D; Mischianu, D**. *Human papilloma virus infection in men-topographical and procedural aspects-a systematic review*. Revista Română de Urologie, 2016, 15(4): 23-27.
42. **Spinu, D; Bratu, O; Marcu, D; Niculae, A; Geavlete, B; Diaconu, C; Mischianu, D**. *HPV and bladder cancer-is there a connection?*. Modern Medicine, 2017, 24(1): 1-4.
43. **Cozma, CN; Raducu, L; Avino, A; Scaunasu, RV; Bratu, O; Marcu, DR; Jecan, CR**. *A rare case of vulvar squamos cell carcinoma; case presentation*. Journal of Clinical and Investigative Surgery, 2018, 3(1): 32-36.

44. **Stanescu, AMA; Grajdeanu, IV; Bratu, OG; Iancu, MA; Codreanu, IF; Bejan, GC; Diaconu, CC**. *Genetic and therapeutic novelties in atopic dermatitis*. Romanian Journal of Medical Practice, 2018, 13(2): 108-113.
45. **Iorga, L; Anghel, R; Manea, M; Marcu, D; Socea, B; Diaconu, C; Bratu, O; Baleanu, V-D; Mischianu, D**. *Necrotizing fasciitis of the male genital region – a review of the literature*. Research and Science Today, 2018, suppl 2: 24-36.
46. **Manea, M; Marcu, D; Diaconu, C; Socea, B; Dimitriu, M; Baleanu, V-D; Bratu, O.** *Thromboprophylaxis in surgical patients*. Research and Science Today, 2018, suppl 2: 57-65.
47. **Socea, B; Halau, O; Diaconu, C; Bratu, OG; Neagu, TP; Dimitriu, M; Constantin, VD**. *Clostridium difficile infection in surgical patients (literature review)*. Romanian Journal of Medical Practice, 2019, 14(1): 30-33.
48. **Constantin, Vlad; Socea, Bogdan; Moculescu, Cezar; Sireţeanu, George; Popa, Florin;** *Enteral non-Hodgkinian lymphoma in young age – difficult diagnostic.* Chirurgia, 2009, 104(5): 601-604.
49. **Wiltz, OH; Torregrosa, M; Wiltz, O**. *Autogenous vaccine: the best therapy for perianal condyloma acuminata? Dis Colon Rectum.*, 1995, 38: 838.
50. **Tian, YP; Yao, L; Malla, P; Song, Y; Li, SS**. *Successful treatment of giant condyloma acuminatum with combination retinoid and interferon therapy*. *Int J STD AIDS.*, 2012 , 23(6): 445.