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Extramammary Paget's Disease Manifested by Intraepithelial Adenocarcinoma of the Vulva and Anus Combined with Invasive Adenocarcinoma of the Ampullary Part of the Rectum

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Abstract

The Object of the Study: The author of the given paper describes an unusual combination of two diseases: extramammary Paget's disease manifested by intraepithelial adenocarcinoma of the vulva and anus combined with invasive adenocarcinoma of the ampullary part of the rectum and describes the atypical manifestations of these diseases. **The Content:** The content of this research paper includes a description of the patient, an analysis of the clinical picture, diagnostic methods and therapeutic interventions used, a report of the following disease, and the result of the presented case. **The Result of the Research Work:** The result of the research work is the analysis of a clinical case with two different tumors, where such a combination of tumors is rarely described in the literature. Moreover, no large specific sample with this combination of diseases is available. **Patient Characteristics:** The given case report describes a patient of the Palliative Care Unit of the Gerontology Clinic with a primary diagnosis of C20-rectal adenocarcinoma in the background of the anal canal, perineal skin Paget's disease, stage IV. The presented complications of the patient's primary diagnosis are multiple metastases in the liver; status post palliative chemotherapy; hepatomegaly; metastases to abdominal lymph nodes, inguinal lymph nodes; metastases at Th12, L4 level; pain syndrome. The presented above combination of diagnosed diseases is very rare. **Applied Diagnostics:** In October 2021, it was performed diagnostic manipulation: biopsy and the pathologist have provided a microscopic description. The first tissue fragment had a pronounced electrothermal lesion and the epithelial structures were not valuable. The second skin tissue fragment was

covered with hyperplastic and acanthotic epithelium; its basal and middle layers contained multiple large cells proliferates extending into the medial epidermis, and the cytoplasm of these cells reacted positively with PAS (Periodic Acid Schiff reaction). It needs to be noted that the patient had previously had several years of biopsies from the perineal and anal epidermis, where Paget's disease had also been diagnosed. The performed immunohistochemistry showed these cells to be CK20 positive, CK7 rare positive and p16 negative. The following pathohistological findings were made: morphological and immunohistochemical picture is consistent with Paget's disease. According to the ICD-10, the patient was diagnosed with C51 malignant neoplasm of the female external genitalia. Using imaging diagnostics, it became clear that the patient's rectal adenocarcinoma had progressed to metastatic stage with distant liver metastases in the background of anal canal, perineal skin Paget's disease. **Therapeutic Plan of the Patient:** Based on the patient's main diagnoses, the complications of the principal diagnosis, the patient's overall severe condition, pain syndrome, age and comorbidities, palliative chemotherapy was approved as a therapeutic option in council of doctors. **Monitoring and Outcome of the Patient:** The patient's general condition was becoming worse over time, and she was diagnosed with exitus latalis in December 2022. At that time, the patient was discharged from hospital and was on palliative care at home under the control of her family physician.

Keywords

Extramammary Paget's Disease, Intraepithelial Adenocarcinoma of the Vulva and Anus, Invasive Adenocarcinoma of the Ampullary Part of the Rectum, Biopsies from the Perineal and Anal Epidermis, Malignant Neoplasm of the Female External Genitalia

1. Introduction

The author of the given paper describes an unusual combination of two diseases: extramammary Paget's disease manifested by intraepithelial adenocarcinoma of the vulva and anus combined with invasive adenocarcinoma of the ampullary part of the rectum and describes the atypical manifestations of these diseases.

The object of this study is a specific clinical case and its rarity.

Extramammary Paget's disease is rare, with an incidence estimated to be 0.11 per 100,000 person years. Of all cases of Paget disease (mammary and extramammary), extramammary Paget's disease accounts for 7% to 14%. The age of onset of extramammary Paget's disease is typically 64 to 75 years. White women and Asian men are affected at disproportionately high rates. The vulva is the most involved site of extramammary Paget's disease, accounting for approximately 65% of extramammary Paget's disease [1].

In contrast to extramammary Paget's disease, the incidence of rectal adenocarcinoma is high. Colorectal cancer accounts for approximately 10% of all an-

nually diagnosed cancers and cancer-related deaths worldwide. It is the second most common cancer diagnosed in women and the third most in men. In women, incidence and mortality are approximately 25% lower than in men. With continuing progress in developing countries, the incidence of colorectal cancer worldwide is predicted to increase to 2.5 million new cases in 2035. A worrying rise in patients presenting with colorectal cancer younger than 50 years has been observed, especially rectal cancer and left-sided colon cancer. Although genetics, lifestyle, obesity, and environmental factors might have some association, the exact reasons for this increase are not completely understood [2].

In the present study, a detailed case report, which will include the results of morphological examinations, will be presented. The study will contain a retrospective analysis of the autopsy protocol, histological specimens, and clinical information.

Relevance of the study: the incidence of colon oncological diseases is increasing in Latvia now. Therefore, it is important to recognize various non-invasive and invasive oncological diseases to detect oncological processes at early stages, initiate early prevention, and diagnosis, apply appropriate treatment methods and avoid incorrect diagnosis therapy, thus improving the quality of life of patients and generally prolonging the survival of the population. Adenocarcinoma is the most common form of colon malignancy, and rare cases of concurrent diagnosis of other morphological variants have been described before.

The aim of this case report is to provide a deep, detailed and comprehensive description of a specific manifestation of extramammary Paget's disease with vulvar and anal intraepithelial adenocarcinoma in combination with invasive rectal adenocarcinoma.

Objectives of Study

1) To summarize the literature sources on the topic of Paget's disease, its forms, morphology, and epidemiology.

2) To summarize the literature sources on rectal (colorectal) adenocarcinoma, its morphology and epidemiology.

3) To study the morphology of a case report of extramammary Paget's disease.

4) To provide a description of a definite patient, the clinical presentation and the diagnostic methods which have been used.

The content of this research paper includes a description of the patient, an analysis of the clinical picture, diagnostic methods and therapeutic interventions used, a report of the following disease, and the result of the presented case.

The result of the research work is the analysis of a clinical case with two tumors, where such a combination of tumors is rarely described in the literature. Moreover, no large specific sample with this combination of diseases is available.

2. Patient Characteristics

The given case report describes a patient of the Palliative Care Unit of the Gerontology Clinic with a primary diagnosis of C20-rectal adenocarcinoma in the

background of the anal canal, perineal skin Paget's disease, stage IV. The presented complications of the patient's primary diagnosis are multiple metastases in the liver; status post palliative chemotherapy; hepatomegaly; metastases to abdominal lymph nodes, inguinal lymph nodes; metastases at Th12, L4 level; pain syndrome.

The presented above combination of diagnosed diseases is very rare.

The rarity of extramammary Paget's disease can be demonstrated by statistical data. Based on the data of the Center for Disease Prevention and Control, extramammary Paget's disease with morphological code M8542/3 was reported in one case in 2018 with diagnosis code C44.5 (ICD-10). The patient of this case is currently alive. Rectal malignancy is a relatively common disease with a high mortality rate, as evidenced by the data of the Center for Disease Prevention and Control. Table 1 and Table 2 show the reported cases and the number of deaths from rectal adenocarcinoma [3].

The patient of the given clinical case is a 75-year-old pensioner. The general condition of the patient at the time of hospitalization is moderate.

The patient was urgently admitted to the Admissions Department of RAKUS "Gaiļezers" with complaints of severe colicky pain in the perineum; this type of pain has intensified in the last few days. The patient noted a poor appetite. This is not a first occurrence, and the patient has been under the care of medical oncologists for two years.

It is known from the medical records that the patient was previously hospitalized to the Department of Abdominal and Soft Tissue Surgery in the Oncosurgery Clinic in October 2021, where a repeat biopsy of the anal canal and perineal skin was ordered, as well as an MRI scan before starting chemotherapy.

Table 1. Incidence of rectal adenocarcinoma (C20, M8140/3, M8010/3) [3].

Year	Number of cases
2017	219
2018*	260
2019*	228

*Due to the interruption in the Registry's operations, data for 2018 and 2019 are provisional.

Table 2. Number of deaths diagnosed as rectal adenocarcinoma (C20, M8140/3, M8010/3) with underlying cause of death C20 [3].

Year of death	Number of deaths
2017	26
2018	60
2019	83
2020	77
2021	38

Later, in March 2022, a repeat oncology confirmed Paget's disease of the anal canal and perineal skin with multiple liver metastases in both lobes. Due to the above, the patient received palliative chemotherapy.

3. Clinical Findings

3.1. Extramammary Paget's Disease Clinic

The lesions in extramammary Paget's disease are nonspecific and multiple topical therapies are often tried before the diagnosis is made. A median delay of 2 years has been reported. The primary lesion is an erythematous and scaly plaque, usually well delineated, and may demonstrate crusting, weepy erosions, and even ulcerations. Infiltrated nodules, vegetative lesions, and regional lymphadenopathy may be present. Pigmentary changes may also be noted, more often hypo-rather than hyperpigmentation. Lesions are often solitary, but may be multiple, in which cases the plaques seem to be separated by areas of normal skin. Patients often complain of pruritus (up to 60% - 72%), but burning, tenderness, and edema may be experienced as well. Up to 39% of patients may have associated lymphadenopathy, either unilateral or bilateral [4].

3.2. Clinic for Adenocarcinoma of the Rectum (Colon)

Patients can present with a wide range of signs and symptoms such as occult or overt rectal bleeding, change in bowel habits, anemia, or abdominal pain. However, colorectal cancer is largely an asymptomatic disease until it reaches an advanced stage. By contrast, rectal bleeding is a common symptom of both benign and malignant causes, and therefore additional risk factors might be needed to help identify those people who should undergo further investigation by colonoscopy [2].

3.3. Clinical Findings of the Patient

The patient in the clinical case, in addition to the above-mentioned non-specific symptomatology, lymphadenopathy, local discomfort in the affected vulvar and anus region, also developed unexplained weight loss to cachectic state, malaise, weakness over a period of years. The local condition was like the local visualizations of extramammary Paget's disease found in the literature (**Figure 1**).

4. Applied Diagnostics

Diagnosis and definitive treatment are often delayed due to the non-specific clinical findings resulting in misdiagnosis, and elderly patients frequently present late. Extramammary Paget's disease is commonly mistaken for: contact dermatitis, fungal infection, psoriasis seborrheic dermatitis, anogenital intraepithelial neoplasia, Lichen sclerosis, melanoma, mycosis fungoides, and histiocytosis. Perianal or vulvar extramammary Paget's disease may also be misdiagnosed as leukoplakia, squamous cell carcinoma, basal cell carcinoma, condylomata acuminate, hidradenitis suppurativa, or Crohn's disease [5].

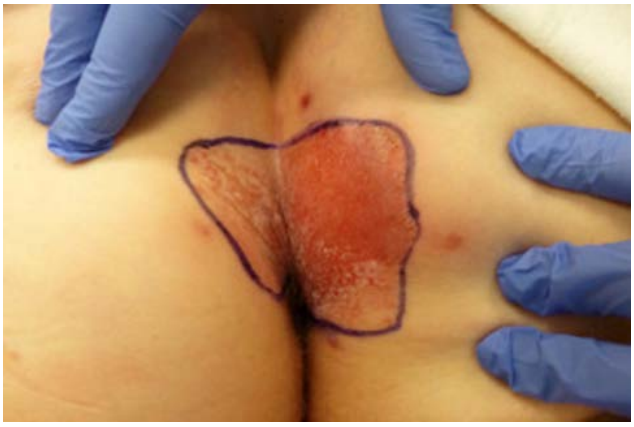

Figure 1. Typical clinical picture (erythematous, scaly plaque in the intergluteal region) [1].

Diagnosis of extramammary Paget's disease must be confirmed by histologic examination. Moreover, underlying neoplasm should be ruled out by complete pelvic examination, colposcopy and radiologic examination [6].

4.1. Biopsy and Histological Confirmation of the Diagnosis

Paget tumor cells are in the epidermis. Rarely, tumor cells can extend into the dermis. The Paget cells are located near to the basement membrane, and they extend to fill the entire epidermis as the condition progresses. Tumor cells are large with clear or eosinophilic cytoplasm, large pleomorphic nuclei and occasional mitoses (**Figure 2**). Ulceration and pigmentation may be present. Dermal changes include a chronic inflammatory infiltrate [7].

In October 2021, it was performed diagnostic manipulation: biopsy and the pathologist have provided a microscopic description. The first tissue fragment had a pronounced electrothermal lesion and the epithelial structures were not valuable. The second skin tissue fragment was covered with hyperplastic and acanthotic epithelium; its basal and middle layers contained multiple large cells proliferates extending into the medial epidermis, the cytoplasm of these cells reacted positively with PAS (Periodic Acid Schiff reaction). It needs to be noted that the patient had previously had several years of biopsies from the perineal and anal epidermis, where Paget's disease had also been diagnosed.

Unlike the majority of cases of mammary Paget disease, the Paget cells in extramammary Paget disease contain ample mucin, which may be confirmed by staining with Alcian blue, mucicarmine, Periodic acid-Schiff (PAS), and colloidal iron. Immunohistochemistry is often used to diagnose Paget disease and to identify the likely cell of origin. Paget cells usually stain for markers of eccrine and apocrine derivation including low molecular weight cytokeratins (CK), periodic acid-Schiff (PAS), *gross cystic disease fluid protein* (GCDFP-15), and carcinoembryonic antigen (CEA). S100 staining is negative [5].

The performed immunohistochemistry showed these cells to be CK20 positive, CK7 rare positive and p16 negative. The following pathohistological find-

ings were made: morphological and immunohistochemical picture is consistent with Peget's disease. According to the ICD-10, the patient was diagnosed with C51 malignant neoplasm of the female external genitalia.

CK7 is the most useful marker as it is not expressed by the surrounding epidermal cells. BerEp4 has been proposed as a useful marker, because extramammary Paget disease cells are 100% positive. High molecular weight cytokeratin (HMWCK) and p63 are useful complementary markers, because squamous carcinoma in situ is nearly always positive while Paget cells are nearly always negative [8].

In secondary Paget disease the phenotype may depend upon the nature of the underlying carcinoma. Most cases with underlying rectal adenocarcinoma are reported to be CK7 and CK positive [6].

The literature also describes an approach to initial histological assessment in Paget's disease (**Figure 3**).

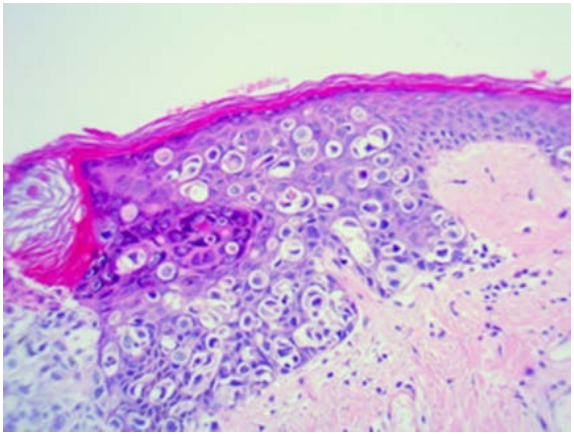

Figure 2. Paget tumour cells in the epidermis (×20) [7].

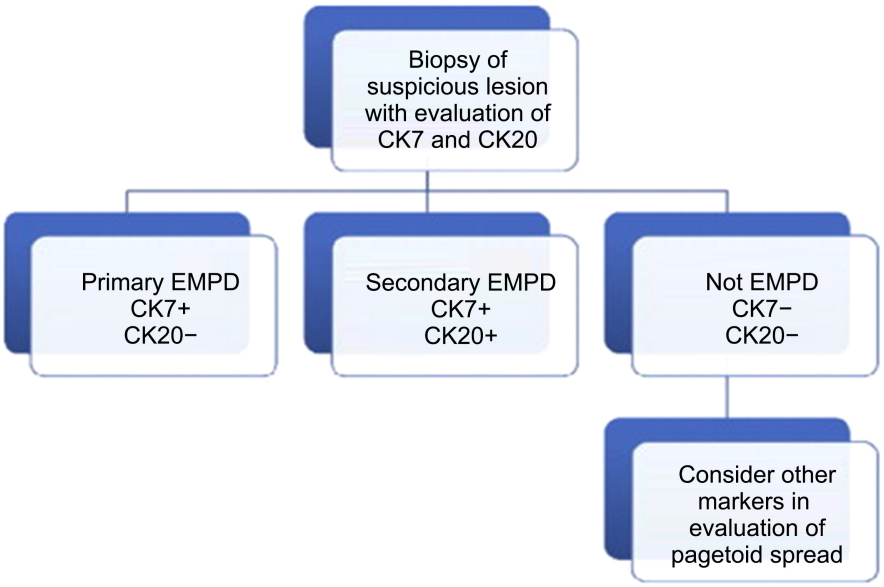

Figure 3. Approach to initial histological evaluation [4].

4.2. Imaging Examinations

Imaging examinations are mainly performed to clarify the spread of the malignant process, to detect abnormalities in the patient's existing internal organs and to observe the dynamics of the pathological process. Depending on the localisation of the lesions, the following examinations should be performed: rectocolonoscopy, cystoscopy, abdominal ultrasound or CT scan, gastroduodenal fibroscopy, mammography.

In September 2021, the patient underwent a magnetic resonance examination of the small pelvis as it was ordered by the consilium. The MRI findings suggested a malignant process in the anal canal and supra-anal with involvement of the internal sphincter and metastatic lymph nodes in the adipose tissue of the mesorectal space.

The patient also underwent additional investigations such as computed tomography of the abdomen and lungs. Also, a repeat computed tomography was performed after chemotherapy.

In October 2021, the patient underwent a CT scan of the abdomen. The radiologist has given his conclusion. Metastases were found in the liver. The liver is of normal size and density (+53 HV), smooth. Both lobes show separate hypodense foci with unclear contours: Sg2/4a border ventrally 0.7 × 0.5 cm, Sg5 laterally 1.5 × 1.3 cm, Sg3 laterally 0.7 × 0.5 cm. Metastatic lymph nodes in the adipose tissue of the mesorectal space and multiple cysts in both kidneys and liver are also described. A myoma uteri is also visualised on CT examination.

Using imaging diagnostics, it became clear that the patient's rectal adenocarcinoma had progressed to metastatic stage with distant liver metastases in the background of anal canal, perineal skin and Paget's disease.

5. Therapeutic Plan of the Patient

The treatment of extramammary Paget's disease has long been surgical excision with adjuvant therapies in select cases. Mohs micrographic surgery (MMS) has emerged as a promising therapeutic option as it offers complete evaluation of tissue margin, maximal tissue preservation, and the lowest recurrence rates. However, it is limited by ill-defined clinical margins, microscopic extension of tumor cells, multifocal disease, and sometimes lesion size given the outpatient nature of MMS [9].

Based on the patient's main diagnoses, the complications of the principal diagnosis, the patient's overall severe condition, pain syndrome, age and comorbidities, the palliative chemotherapy was approved as a therapeutic option in council of doctors.

It should be mentioned here that the literature data shows that systemic chemotherapy is not very effective in metastatic extramammary Paget's disease.

Systemic chemotherapy has shown little efficacy in the treatment of metastatic disease. Several regimens have been used to treat metastatic extramammary Paget's disease, including low-dose 5-fluorouracil/cisplatin, FECOM (5-fluorouracil, ep-

irubicin, carboplatin, vincristine, and mitomycin C), docetaxel mono therapy, S-1 monotherapy, docetaxel and S-1 combination therapy, and PET (cisplatin, epirubi cin, and paclitaxel). Complete cure has not been obtained, but improved quality of life has been achieved with minimal treatment-related morbidity [1].

The systemic treatment of patients with colorectal cancer is regarded as palliative when their disease is found to be metastatic, or to be locally advanced and inoperable (**Figure 4**). In this setting, the aim of treatment is to achieve control of disease in order to prolong survival, with a particular emphasis on treating or preventing cancer-related symptoms and on maintaining quality of life [10].

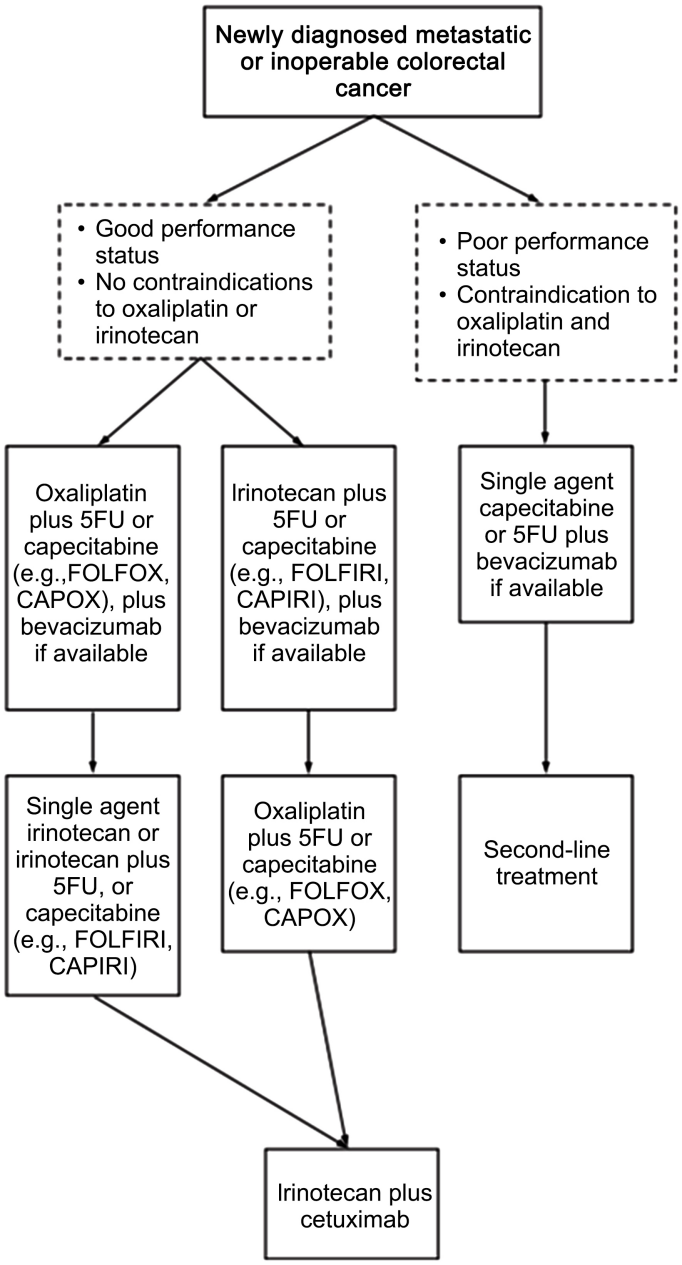

Figure 4. Treatment of patients with metastatic or inoperable colorectal cancer [10].

The combination and sequence of drugs used for systemic therapy of colorectal cancer is shown below.

In the past decade, the systemic treatment options for advanced colorectal cancer have expanded from the use of single agent 5-fluorouracil (5FU) chemotherapy to three active cytotoxic agents (5FU and other fluoropyrimidine analogs, oxaliplatin, and irinotecan), as well as the novel targeted therapies, bevacizumab and cetuximab. With the different combination and treatment sequencing options available, patients with this disease are achieving median survivals in excess of 20 months in clinical trials [10].

In February 2022, the patient received the following chemotherapy drugs: Leucovorin 320 mg, Oxaliplatin 135 mg, 5-FU (5-fluorouracil) 640 mg and 1000 mg. The combination of these drugs is mainly aimed at the treatment of colorectal cancer.

The patient did not come to her next course of palliative chemotherapy in hospital in March 2022.

As the disease progressed, the patient was prescribed palliative care, symptomatic therapy and prophylactic measures. Additionally to maintenance infusion therapy, such remedy as *Dexamethasone* was prescribed to reduce inflammatory reactions. To alleviate the patient's severe condition an adequate analgesic therapy—transdermal patches *Matrifen* (Fentanyl), *Gabapentin, Amitriptyline* were prescribed to the patient. *Clonazepam* was prescribed to stabilise the patient's neurological condition and *Cerucal* was prescribed for nausea.

6. Monitoring and Outcome of the Patient

The patient's general condition was becoming worse over time and she was diagnosed with exitus latalis in December 2022. At that time, the patient was discharged from hospital and was on palliative care at home under the control of her family physician. The General Practitioner referred the patient for autopsy. The autopsy was performed three days after death.

The following data about the patient are known from the autopsy report.

The internal examination of the patient revealed atherosclerotic changes such as fibrous plaques in the aorta, coronary arteries and cerebral arteries. Heart with small connective tissue fibers.

Liver 3100 g with confluent metastases in both lobes from 0.6 to 6.0 cm in diameter. Metastases pale in section.

In the pleura of both lungs, lung tissues (on both sides in all lobes) are metastases between 0.5 and 2 cm in diameter.

Parabronchial, mediastinal, hepatic, inguinal, mesenteric lymph nodes enlarged up to 3.5 cm in diameter, in places forming bundles.

Both kidneys with small retention cysts 0.4 - 0.6 cm in diameter.

Spleen 85 g, greyish pink.

Brain 1250 g, slight edema is observed.

Pancreas with autolytic changes.

Small intestine without pathological changes. Appendix 4 × 0.5 cm.

Caecum, colon ascendens, descendens and sigma without pathological changes. In the rectum, 2 cm above the sphincter, a tumor 6.4 × 6.2 cm in size has appeared, which visually penetrates the wall of the intestine.

Skin of perineum, vulva, anus with superficial erosive surface, no compactions are detected.

The histological findings of the specimens are the following:

- Skin from vulva, anal region-epidermis with atrophy and erosions is observed. In places, atypical epithelioid, enlarged cells are found in the basal layer of the epidermis (Figure 5). Dermis with mild fibrosis, periocular infiltration of lymphocytes.
- Tissues from the rectum above the sphincter are observed tumor complexes made of atypical epithelial cells, sometimes solid, sometimes tubular in structure. Tumor cells are found in the mucosa, submucosa, muscularis mucosae and pararectal tissues (Figure 6, Figure 7). Invasion of tumor masses into lymph ducts, perivascular growth is observed. Atypical epithelial cells in the basal part of the squamous epithelium are found at the border between the mucocutaneous glandular epithelium and the multilayered squamous epithelium.
- Liver with tumor metastases composed of atypical epithelial cells, sometimes solitary, sometimes tubular (Figure 8).
- Analogous metastatic tumor complexes are observed in the lungs and regional lymph nodes (Figure 9).
- Micrometastases have also been found in the brain.

The autopsy led to two working diagnoses:

1) Paget's disease with development of invasive carcinoma.

2) Or two different tumors—Paget's disease and invasive adenocarcinoma of the colon.

Immunohistochemistry is not used in autopsy material because the NHS tariff does not cover the cost of immunohistochemistry examinations. In addition to it, several days had passed since the patient's death and autolysis had started, which may also affect the immunohistochemistry result.

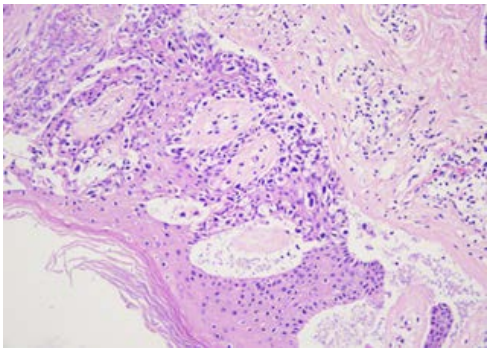

Figure 5. Autopsy preparation: Epidermis with Paget cells in the basal layer (×20).

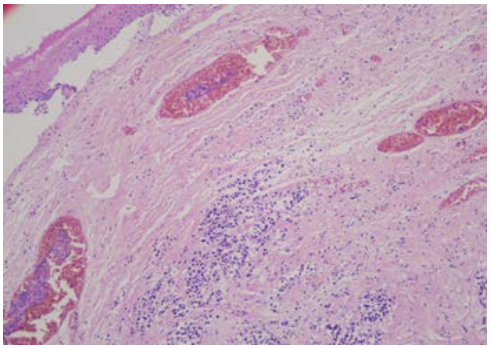

Figure 6. Autopsy preparation: The invasive component in the intestinal wall.

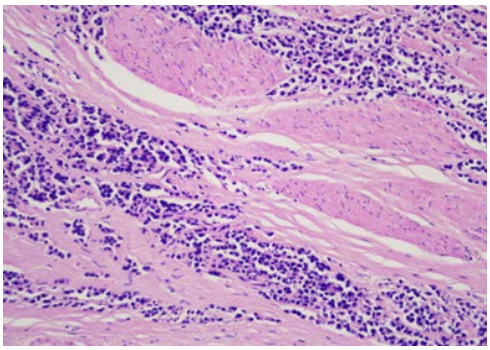

Figure 7. Autopsy preparation: Tumor invasion in the muscular layer of the intestine.

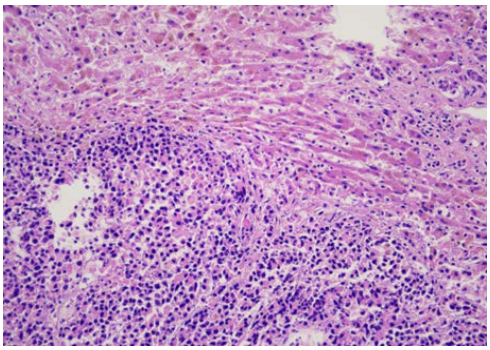

Figure 8. Autopsy preparation: Liver metastases.

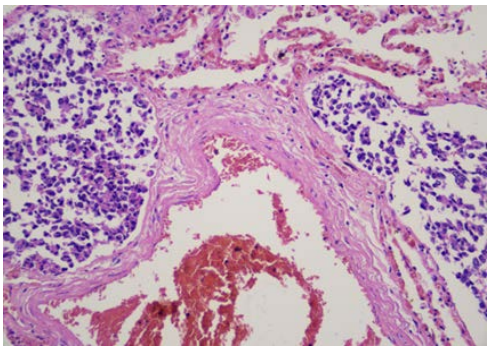

Figure 9. Autopsy preparation: Lung metastases.

The tumor cells detected on histological examination were small, monomorphic, but with glandular structures both in the primary location and in the metastases. Colonic adenocarcinoma is usually composed of longer, cylindrical cells with glandular structures. From the biopsy findings, the tumor was known to express CK20 and to some extent CK7. Considering the above, the morphological picture is consistent with Paget's disease with the development of invasive growth and formation of GIII invasive adenocarcinoma in the distal part of the colon.

Considering the tumor growth pattern, cell type and previous biopsy findings, the final pathanotomy diagnosis the following diagnosis was made:

1) Extramammary anal and vulvar Paget's disease with invasion into the dermis, mucosa. Invasive GIII adenocarcinoma of the colon (apT3N2M1 GIII).

2) Metastases in liver, lungs, brain.

3) General atherosclerosis, mostly in the aorta, coronary arteries.

7. Discussion and Patient Perspective

7.1. Discussion and Perspective Linking the Case Study to Cases Reported in the Sources of Literature

Patients diagnosed with extramammary Paget's disease must be risk stratified. Ambiguity exists within the literature regarding risk for associated malignancies; an associated underlying internal cancer has been reported in 7% - 40% of patients with extramammary Paget's disease. Most reported cases of internal malignancy are in close proximity to the cutaneous extramammary Paget's disease. Therefore, a directed internal malignancy evaluation is appropriate. Dependent on gender, appropriate studies to consider include mammography, pelvic ultrasonography, cystoscopy, colonoscopy, and computed tomography of the abdomen and pelvis [9].

Close clinical follow-up of patients with extramammary Paget's disease is recommended due to recurrence risk. Biannual evaluation for at least 3 years, then annually for at least 10 years for non-invasive extramammary Paget's disease, has been suggested. In invasive extramammary Paget's disease or cases associated with a distant, underlying tumor, follow-up should be more frequent with a low threshold to biopsy any suspicious skin lesion. In general, patients with extramammary Paget's disease have a good prognosis with a 5-year overall survival of 75% - 95%. Dermally invasive extramammary Paget's disease is more frequently associated with regional lymph node metastasis and poor prognosis [9].

7.2. Discussion of the Diagnostic Challenges

The typical appearance of extramammary Paget's disease is single or multifocal erythema and a hypo- or hyperpigmented plaque in the genital area. The margin of tumour is sometimes ill-defined especially in vaginal mucosa and this is associated with high local recurrence rates after surgery (16% - 44%). Moreover,

eroded extramammary Paget's disease lesions are frequently complicated by bacterial and fungal infections, making the clinical margins more indistinct [11].

Biopsy should be performed immediately upon suspicion of extramammary Paget's disease. Histologically, extramammary Paget's disease is characterized by intraepidermal proliferation of Paget cells (PCs), which have large vesicular nuclei and abundant pale cytoplasm. Extension into adnexal structures is common and may be misinterpreted as dermal invasion. In addition to hematoxylin and eosin, diagnosis is confirmed by utilizing a panel of immunoperoxidase studies including cytokeratin 7, carcinoembryonic antigen, epithelial membrane antibody, HER-2/neu, and gross cystic disease fluid protein-15. These can be used to differentiate extramammary Paget's disease from pagetoid variants of squamous cell carcinoma in situ and melanoma in situ. The expression of tissue-specific antigens within PCs appears to correlate with that of the underlying malignancy: prostatic antigen, uroplakins, and transcription factor CDX-2 in prostatic, urothelial, and intestinal adenocarcinomas, respectively. However, limitations to the use of tissue-specific markers necessitate careful clinicopathologic correlation [9].

7.3. Limitations and Disadvantages of the Chosen Therapy

Surgery is still considered the gold standard of treatment for patients with extramammary Paget's disease. Over the years, many therapeutic modalities have been attempted on patients with extramammary Paget's disease to reduce the significant morbidity associated with the often-radical surgical treatments performed. Because of the rarity of this condition, experience in its management is limited. Due to the high frequency of recurrences after excision, adjunctive therapy is often used. The literature recommends a safety resection margin of 2 cm, although a 1 cm margin could be sufficient for lesions with clinically clear margins. A lower recurrence rate has been reported when utilizing Mohs micrographic surgery (a recurrence rate of 23% for MMS versus 33% for conventional excision with margin control). Systemic chemotherapy (vincristine, docetaxel, carboplatin, 5-FU, mitomycin-C, etoposide) can be used if there are contraindications to surgery and radiotherapy. Radiation treatment can be utilized for inoperable lesions or as adjuvant treatment to surgical excision, namely, in the case of postoperative recurrence; the results are better in primary in situ extramammary Paget's disease. Local application of cytotoxic drugs (bleomycin, 5-fluorouracil) alone is not sufficient, but may decrease the margins of the lesions or assist in visualization, rendering resection more efficacious. The topical immune-response modifier, imiquimod, has been successfully used in a small number of extramammary Paget's disease cases it appears to be helpful in superficial forms. Imiquimod can be considered an alternative to surgery, an adjunct before or after surgery, and even part of a therapeutic combination with other treatment modalities [5].

According to the data of the described studies, for systemic metastases, in-

cluding extensive lymph node metastases, no systemic chemotherapy improved a patient's survival. Moreover, as most patients with extramammary Paget's disease are elderly, the indication for systemic chemotherapy is frequently limited. Taking these factors into consideration, at present, surgical resection of lymph node metastasis, before lymphatic spreading, may be the most promising strategy to prevent tumour-related death [9].

7.4. Findings Obtained as a Result of Research

The invasion level was the most significant factor associated with a decreased overall survival. In contrast to the invasion level, tumour size was not associated with poor prognosis [11].

Because of extramammary Paget's disease is frequently located medially in the genital region, sentinel nodes may be present in bilateral inguinal regions. Extensive lymph node metastases were sometimes accompanied by bilateral inguinal erythema (underpants-pattern erythema), which is caused by lymphatic infiltration by extramammary Paget's disease tumour cells [11].

Serum level of CEA is known to be a useful tumour marker for adenocarcinomas such as colon cancer. As extramammary Paget's disease shares certain characteristics with adenocarcinomas, it is not surprising that elevated serum CEA levels have been reported in patients with extramammary Paget's disease with systemic metastases. However, all patients who showed high serum CEA levels revealed systemic extramammary Paget's disease metastases. The sensitivity was relatively low, serum CEA level could serve as a marker of systemic metastasis and response to treatment [11].

In conclusion, as most extramammary Paget's disease cases have a favourable prognosis, the major purpose of treatment for noninvasive disease is local tumour control. Surgical excision with careful evaluation of the tumour margin is the most common treatment; however, an extensive margin is not associated with a lower risk of local recurrence. Invasion level and multiple lymph node metastases are important prognostic factors in extramammary Paget's disease. Thus, a tumour-node-metastasis (TNM) classification should be adapted according to the unique clinical features of extramammary Paget's disease. As no effective therapy is available for widely metastatic disease, the therapeutic strategy for advanced extramammary Paget's disease requires further investigation [11].

8. Conclusions

- Extramammary Paget's disease is rare pathology, with an incidence estimated to be 0.11 per 100 000 person years. Of all cases of Paget disease (mammary and extramammary), extramammary Paget's disease accounts for 7% to 14%.
- The vulva is the most involved site of extramammary Paget's disease, accounting for approximately 65% of extramammary Paget's disease.
- Rectal malignancy is a relatively common disease with a high mortality rate.

The incidence of rectal adenocarcinoma is high. Colorectal cancer accounts for approximately 10% of all annually diagnosed cancers and cancer-related deaths worldwide.

- Diagnosis is difficult in the case of extramammary Paget's disease, because the lesions are nonspecific and multiple topical therapies are often tried before the diagnosis is made.
- Diagnosis of extramammary Paget's disease must be confirmed by histologic examination and immunohistochemistry must be performed.
- In general, patients with in situ extramammary Paget's disease have a good prognosis with a 5-year overall survival of 75% - 95%. Dermally invasive extramammary Paget's disease is more frequently associated with regional lymph node metastasis and poor prognosis.
- The given case report describes a patient of the Palliative Care Unit of the Gerontology Clinic with a primary diagnosis of C20-rectal adenocarcinoma in the background of the anal canal, perineal skin Paget's disease, stage IV. The presented above combination of diagnosed diseases is very rare.
- In March 2022, repeat oncology confirmed Paget's disease of the anal canal and perineal skin with multiple liver metastases in both lobes. Due to the above, the patient received palliative chemotherapy.
- As the disease progressed, the patient was prescribed palliative care, symptomatic therapy and prophylactic measures.
- The performed immunohistochemistry showed these cells to be CK20 positive, CK7 rare positive and p16 negative. The following pathohistological findings were made: morphological and immunohistochemical picture is consistent with Paget's disease. According to the ICD-10, the patient was diagnosed with C51 malignant neoplasm of the female external genitalia.
- Using imaging diagnostics, it became clear that the patient's rectal adenocarcinoma had progressed to a metastatic stage with distant liver metastases in the background of anal canal, perineal skin and Paget's disease.
- The patient's general condition was becoming worse over time, and she was diagnosed with exitus latalis in December 2022.
- The final patanotomy diagnosis:
- Extramammary anal and vulvar Paget's disease with invasion into the dermis, and mucosa. Invasive GIII adenocarcinoma of the colon (apT3N2M1 GIII).
- Metastases in liver, lungs, and brain.
- General atherosclerosis, mostly in the aorta, and coronary arteries.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Merritt, B.G., Degesys, C.A. and Brodland, D.G. (2019) Extramammary Paget Dis-

ease. *Dermatologic Clinics*, **37**, 261-267. https://doi.org/10.1016/j.det.2019.02.002 https://www-clinicalkey-com.db.rsu.lv/#!/content/playContent/1-s2.0-S0733863519300130?returnurl=null&referrer=null

[2] Dekker, E., Tanis, P.J., Vleugels, J.L.A., Kasi, P.M. and Wallace, M.B. (2019) Colorectal Cancer. *The Lancet*, **394**, 1467-1480. https://doi.org/10.1016/S0140-6736(19)32319-0

[3] Smilga-Veide, A. (2023) Register of Patients with Certain Diseases Diagnosed with Oncological Disease, Latvian Database of Causes of Death, Centre for Disease Prevention and Control. From annika.smilga@spkc.gov.lv, to Anastasia Kursisa to a.kursisa@gmail.com.

[4] Lam, C. and Funaro, D. (2010) Extramammary Paget's Disease: Summary of Current Knowledge. *Dermatologic Clinics*, **28**, 807-826. https://doi.org/10.1016/j.det.2010.08.002 https://www-clinicalkey-com.db.rsu.lv/#!/content/playContent/1-s2.0-S0733863510001270?returnurl=null&referrer=null

[5] McDaniel, B., Brown, F. and Crane, J.S. (2022) Extramammary Paget Disease. In: StatPearls. StatPearls Publishing, Treasure Island. https://www.ncbi.nlm.nih.gov/books/NBK493224/

[6] Nagarajan, P. (2021) Vulva, Vagina & Female Urethra. Other Carcinomas. Paget Disease. https://www.pathologyoutlines.com/topic/vulvapagetsdisease.html

[7] Cheng, H. and Lamont, D. (2014) Extramammary Paget Disease Pathology. https://dermnetnz.org/topics/extramammary-paget-disease-pathology

[8] Stanford University School of Medicine (2009) Surgical Pathology Criteria. Extramammary Paget Disease. https://surgpathcriteria.stanford.edu/dermtumors/extramammary-paget-disease/printable.html

[9] Morris, C.R. and Hurst, E.A. (2022) Extramammary Paget Disease. Treatment of Skin Disease. Comprehensive Therapeutic Strategies. 6th Edition, Elsevier Inc., Amsterdam, 278-280. https://www-clinicalkey-com.db.rsu.lv/#!/content/book/3-s2.0-B9780702082108000828

[10] Brown, G. (2007) Chapter 6-Chemotherapy. *Colorectal Cancer*, **6**, 97-109. https://doi.org/10.1017/CBO9780511902468.007 https://ebookcentral-proquest-com.db.rsu.lv/lib/rsub-ebooks/detail.action?docID=564443#

[11] Hatta, N., Yamada, M., Hirano, T., Fujimoto, A. and Morita, R. (2008) Extramammary Paget's Disease: Treatment, Prognostic Factors and Outcome in 76 Patients. *British Journal of Dermatology*, **158**, 313-318. https://doi.org/10.1111/j.1365-2133.2007.08314.x