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CASE REPORT

Beyond the skin: A case report of vaginal melanoma

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Introduction: Vaginal melanomas account for less than 3% of vaginal neoplasms and are characterized by poor prognosis.

Case report: We present the case of a 65-year-old patient with a history of invasive breast carcinoma and BRAF-negative vaginal melanoma, showing positive immunostaining for S100, SOX-10, PRAME, and vimentin, who was referred to the Dermatology Clinic of Mureș County Clinical Hospital for an erysipelas-like skin reaction on the upper limb affected by chronic lymphedema secondary to axillary lymphadenectomy. Clinical examination revealed diffuse melanosis cutis, acanthosis nigricans, and tripe palms. The patient also exhibited stigmata of Cushing syndrome, with a recent history of systemic corticosteroid therapy. Dermoscopy was performed and revealed dark brown, well defined, round macules on the genital mucosa, while the vaginal mass exhibited dermoscopic signs suggestive of melanoma.

Conclusions: Clinical examination and dermoscopy are essential for patients with mucosal melanomas, as they can uncover details that are critical for creating a comprehensive picture.

Keywords: vaginal melanoma, acanthosis nigricans, diffuse melanosis cutis, tripe palms

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Introduction

Melanoma is a malignant tumor originating from melanocytes in the basal layer of the epidermis, primarily affecting the skin. Mucosal involvement accounts for 1.3% of the melanomas [1]; vaginal melanomas representing only 0.4-0.8% of melanomas in female patients, usually occurring in patients older than 60 [1].

There is a fundamental difference in the pathogenesis of cutaneous and mucosal melanoma – ultraviolet radiation exposure plays a role in cutaneous melanoma tumorigenesis, but not in the other. This distinction explains why the incidence of cutaneous melanomas has increased in past decades while that of mucosal melanomas has remained stable [2]. Compared to other gynecologic cancers, a link between genital melanomas and human papilloma virus (HPV) infection was not established [1].

Clinically, vaginal melanomas present as a pigmented mass on the inferior third of the anterior vaginal wall, with bleeding, vaginal discharge, and dyspareunia as the most common complaints [2]. According to National Comprehensive Cancer Network (NCCN) guidelines, mucosal vulvovaginal melanomas should be staged the same as cutaneous melanomas, and the treatment course is dictated by the resectability of the tumor [3]. Surgical resection with 1 cm tumor-free margins is the ideal treatment, when feasible. Radiation therapy and immunotherapy have shown promising results in combination with surgery; however, the treatment guidelines rely on lower-level evidence due to the scarcity of large-scale studies stemming from the low incidence of the disease [1, 3].

This report aims to present a rare constellation of cutaneous paraneoplastic findings in a patient with metachronous vaginal melanoma and a history of breast cancer, emphasizing the importance of dermatologic signs as potential indicators of underlying malignancy.

Case report

A 65-year-old female patient presented to the Dermatology Clinic of Mures County Clinical Hospital with edema and well-defined erythema of the right hand and forearm, accompanied by local pain and functional impairment. The symptoms had started two days prior to admission, following a minor hand trauma. The diagnosis of erysipelas was established, and the patient was subsequently admitted. The patient signed an informed consent form, permitting the use of personal medical data and images capturing the skin conditions.

Patient's medical history revealed two cancer diagnoses. In 2021, she was diagnosed with stage four invasive carcinoma of no special type (NST) of the right breast, Nottingham grade 2, HER2 - negative, with axillary and paratracheal lymphadenopathy, and a secondary hepatic lesion in segment VI. Given the advanced stage of the disease (T2N1/2M1), first-line chemotherapy for metastatic breast cancer was initiated, with Abemaciclib 150 mg twice daily and Anastrozole 1 mg once a day, resulting in a partial response. Due to persistent pain, palliative bilateral mastectomy and right axillary lymphadenectomy were performed. At the time of the presentation in the Dermatology Clinic, the patient was still undergoing chemotherapy, maintaining a partial remission of the disease.

In 2024, nine months prior to the presentation to the clinic, the patient consulted a gynecologist for vaginal bleed-

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ing. On examination, a solid mass approximately 2 centimeters in diameter was observed on the lower third of the anterior vaginal wall. A pinch biopsy was performed. The histopathological examination reported the diagnosis of melanoma, without determining the primary or metastatic nature of the tumor (Figure 1). Immunohistochemical staining showed positive reaction to S100, SOX-10, PRAME and vimentin, while estrogen receptors, progesterone receptors, GATA3, p16, p63, Pan-CTK, CK AE1/AE3, LCA and chromogranin were negative. Genetic testing for BRAF gene mutation was also negative. Abdominal and pelvic magnetic resonance imaging (MRI), rectoscopy, cystoscopy, and dermatological examination were recommended.

Pelvic MRI revealed a mass of 15 x 8 x 23 mm on the anterior wall of the lower vagina, with no evidence of invasion of the urethra and no evidence of involved lymph nodes, nor distant metastasis. The final diagnostic was stage 2 primary vaginal melanoma. Considering the tumor's location, which greatly restricts the surgical access, its size and the proximity to adjacent anatomical structures, a wide surgical resection with 1 cm clear margin was not feasible. Immunotherapy was initiated with 200 mg of Pembrolizumab intravenous every 21 days. After 3 cycles of Pembrolizumab, the drug was discontinued due to the development of autoimmune pneumonitis. The patient started oral corticosteroid treatment, which subsequently led to iatrogenic Cushing syndrome and associated high blood pressure and osteoporosis. At the time of her presentation to the Dermatology Clinic, Pembrolizumab had been discontinued for five months.

At time of admission, clinical examination revealed chronic lymphedema of the right upper limb following axillary lymphadenectomy. At this site, a diffuse, well-defined erythema was present on the hand and forearm, accompanied by pain and restricted movement. Soft tissue ultrasound showed severe, diffuse edema involving subcutaneous tissue along with signs of lymphangitis.

Stigmata of Cushing syndrome such as dorsocervical fat pad, moon face and abdominal weight gain were evident on clinical examination. A darker, earthy discoloration of the skin was observed, with discrete blue-gray discoloration around the mouth, suggestive of diffuse melanosis cutis (DMC) (Figure 2, 2b).

Velvety brown plaques involving the skin folds (cervical, submammary, lumbar, and inguinal regions), with symmetric distribution, raised the suspicion of paraneoplastic acanthosis nigricans (AN) (Figure 2,3). A 4 mm punch biopsy was proposed; however, the use of anesthetics during chemotherapy was contraindicated by the patient's oncologist. Discrete acanthosis palmaris, also known as tripe palms (TP), was noted, characterized by velvety thickening of the palms and accentuated dermoglyphics (Figure 3a).

A dermoscopic examination was performed. Multiple melanocytic nevi without atypia, seborrheic keratoses, cherry angiomas, and a blue nevus on the left palpebral region were identified. Examination of external genitalia

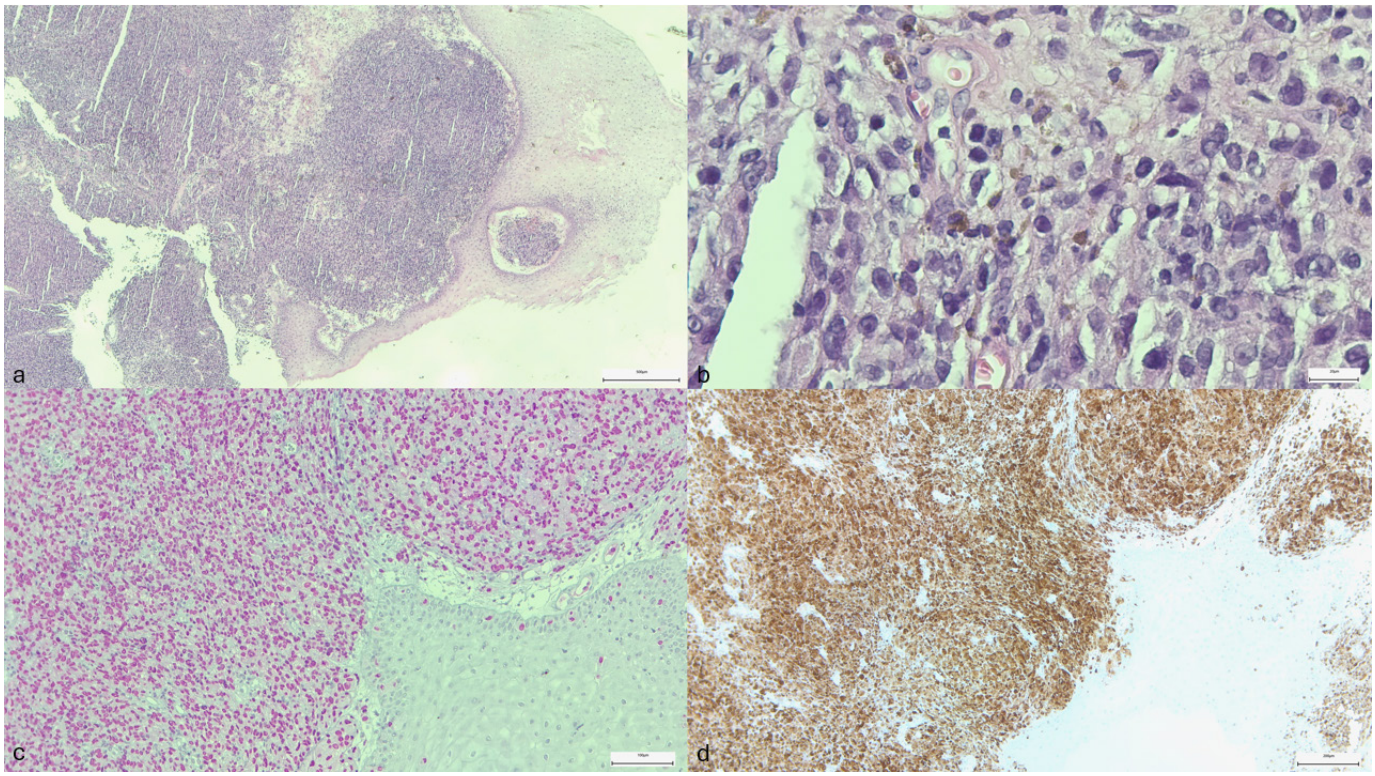

Fig. 1. Vaginal melanoma. Hematoxylin&eosin staining a. (2.5x), b. (40x). Tumoral proliferation composed of monomorphic tumoral cells arranged in nests and sheets, with variably present brown cytoplasmic pigment. Nuclear vesiculation, granular chromatin, and several mitotic figures are observed. The vaginal epithelium contains nests of tumor cells, suggesting intraepithelial extension of the tumor. Immunohistochemistry revealed nuclear positivity for SOX10 (c. 10x) in the tumoral cells and diffuse cytoplasmic and nuclear staining for S100 (d. 4x) in the tumoral cells.

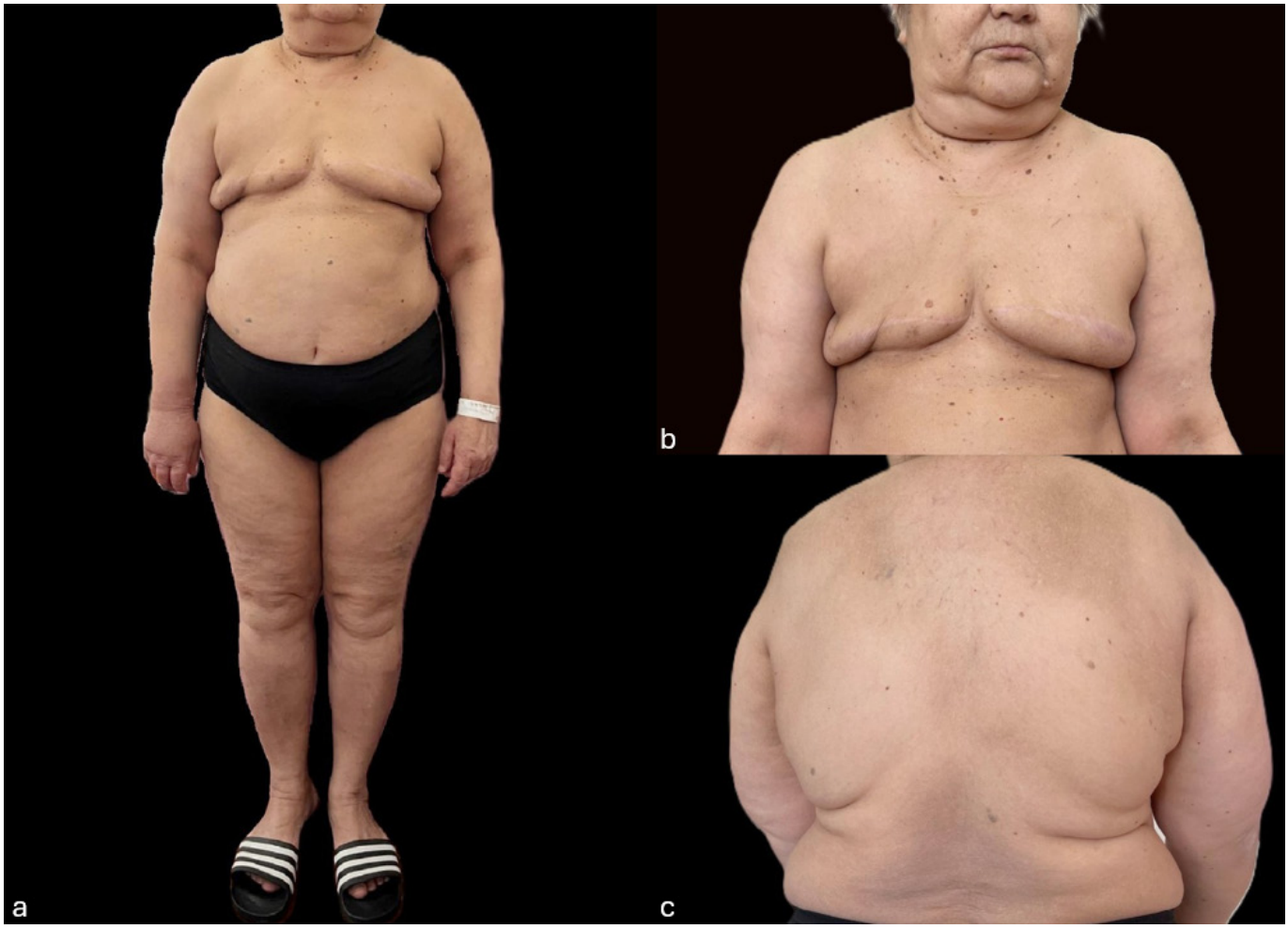

Fig. 2. a. Stigmata of Cushing syndrome; b. and c. DMC (more evident around the mouth) and AN (pictures taken after antibiotic treatment)

revealed dark brown, hypermelanotic, well-defined macules surrounding the urethral hiatus and left labia minora. Dermoscopically, structureless dark brown areas and a white veil were observed when examining the vaginal mass.

Taking all findings into consideration, the current dermatological diagnosis was that of erysipelas-like reaction following minor trauma. The patient was treated with a combination of topical Triamcinolone and Clioquinol ap-

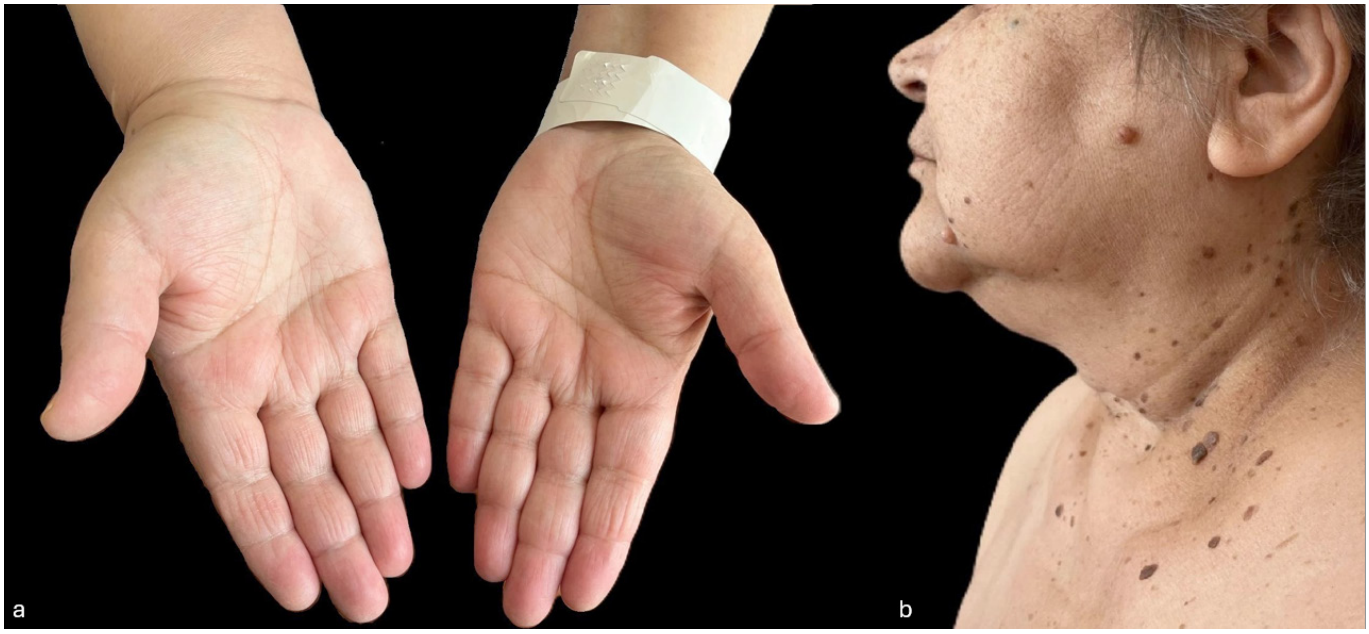

Fig. 3. a. TP and chronic lymphedema of the right upper limb (pictures taken after antibiotic therapy); b. brown, velvety thickening of the epidermis of the neck fold suggesting AN

plied twice daily, along with a 7-day course of Cefuroxime, Desloratadine, and Methylprednisolone 62.5 mg intravenously once daily, with good clinical response during admission with the aforementioned treatment. The patient was discharged with recommendations to continue symptomatic and topical treatment, and to undergo dermoscopic monitoring every three months.

Discussions

Lymphedema and erysipelas

Upper limb lymphedema is a common treatment-related complication in breast cancer patients, particularly those who have undergone axillary lymph node dissection or radiotherapy [4]. This condition, known as breast cancer-related lymphedema (BCRL), stems from impaired lymphatic drainage, leading to edema and progressive fibrosis. As in our case, it develops after cancer therapy and is further influenced by factors like obesity, extensive surgery or genetic predisposition [4,5]. Erysipelas is a frequent complication of BCRL, caused by lymphatic dysfunction and it reflects underlying immunosuppression and often worsens lymphedema, creating a vicious cycle of inflammation and impaired drainage. Effective management and prophylactic measures are key to preventing recurrent infection and limiting disease progression, thereby improving long-term outcomes [5].

Metachronous tumors

Considering the patient's history of breast cancer, the vaginal mass was initially suspected to be metastatic, but it was later ruled out by the histopathological report, which confirmed a different origin of the tumor. Metachronous tumors are defined as a second primary tumor diagnosed six months or more after the initial cancer diagnosis, while synchronous tumors are identified within the six months' timeframe. In breast cancer patients, metachronous tumors occur in 4.1% of cases and are usually diagnosed 58.4 months after the first cancer diagnosis [6]. Our patient developed the second malignancy, the vaginal melanoma, approximately 3 and a half years after the breast cancer diagnosis.

Younger patients are at a higher risk of developing metachronous tumors, with several sites such as thyroid, ovary, lung, bladder or skin being more commonly affected by the second cancer [7]. The association between breast cancer and melanoma was explored; however, most studies refer to cutaneous melanomas, as mucosal melanomas are extremely rare. Exposure to high estrogen levels, such as through hormonal therapy for breast cancer, chemotherapy and radiotherapy may increase the risk of developing cutaneous melanomas, although data is inconsistent. Studies suggest that melanoma and breast cancer share common genetics with certain gene mutations being observed in both cancers (tumor suppressor gene BRCA2 and CDKN2A) [8].

Dermoscopy

Dermoscopy is a valuable diagnostic tool, useful in the initial assessment and in long-term monitoring of patients. According to the NCCN guidelines, a complete skin examination as part of the baseline evaluation for patients diagnosed with vulvovaginal melanoma is advised [3]. When performed by experienced clinicians, dermoscopy provides superior sensitivity and specificity compared to clinical examination in skin cancers' diagnosis, according to a Cochrane systematic review [9].

In the context of vulvovaginal melanoma, dermoscopy plays a critical role in excluding synchronous primary melanomas, cutaneous metastases, or atypical pigmented lesions that might otherwise remain undetected. A particular challenge in diagnosis is amelanotic melanomas, due to the absence of melanin pigmentation, the tumor may be misinterpreted as undifferentiated carcinomas or sarcomas—a diagnostic pitfall documented in the literature [10, 11].

Regular follow-up using digital dermoscopy statistically improves the early identification of in situ and thin melanomas and is particularly recommended for long-term surveillance, especially in high-risk individuals [12]. Regarding surveillance of vaginal melanoma patients, the NCCN guidelines recommend applying the same follow-up protocols used for cutaneous melanoma patients [3]. For cutaneous melanomas, high vigilance is required in the first 1-3 years after treatment, when most metastasis occur, as well as the following 2 years when 4-8% of patients develop another primary melanoma. Follow-up intervals should be individualized based on the initial tumor stage, considering the presence of high-risk factors such as a family history of melanoma or dysplastic nevi. Patients with advanced cutaneous melanomas (stage IIb or higher) should be evaluated every 3 to 6 months in the first 2 years, every 6 to 12 months for the following 3 to 5 years and annually afterwards [13, 14]. Considering the higher risk of cutaneous malignancies in immunocompromised individuals, dermoscopic screening becomes even more crucial for early diagnosis in oncologic patients [15].

Diffuse melanosis cutis (DMC)

DMC is a rare complication of melanoma, associated with poor prognosis and unclear pathophysiology. It is characterized by a progressive alteration of skin color, commonly described as blue-gray, more prominent in sun-exposed areas. DMC is often accompanied by melanuria and is thought to be caused by circulating melanin precursors produced by the primary tumor, which is deposited in the dermis and suffers auto-oxidation. The most important histological feature is the presence of pigment in perivascular melanophages or as free melanin, with no malignant cells appearing in the dermis—distinguishing it from melanoma metastasis [16, 17].

A 2024 systematic review of 61 cases of DMC attempted to define the epidemiology of this entity. DMC was most often reported in Caucasian men in their 50s, with

the primary tumor typically located on the trunk, and the cancer was in an advanced stage. The authors note that the mean survival of these patients is 4 months, significantly lower compared to non-DMC melanoma patients [16]. DMC was rarely reported in mucosal melanomas, and, to our knowledge, this is the first case to be reported in association with vaginal melanoma [18].

Paraneoplastic syndromes

Over 50 skin conditions have been classified as paraneoplastic syndromes. Curth's postulates, elaborated in 1976, defined several criteria for paraneoplastic syndromes: the skin disease must occur and evolve concurrently with the tumor, be rare in the general population but not in oncologic patients, not attributable to a genetic disorder, and show a specific link between a tumor type and a dermatosis [19].

Among paraneoplastic syndromes, AN is one of the best-known. It presents with very distinctive clinical features – symmetric, velvety, hyperpigmented plaques involving the skin folds, often accompanied by acrochordons and occasionally by generalized pruritus [19, 20]. Mucosal involvement, characterized by a verrucous appearance accompanied by hyperpigmentation was reported in 35% of paraneoplastic AN [20].

The pathophysiology of AN is not completely understood. AN often occurs alongside endocrinologic disorders and there is evidence that insulin and insulin-like growth factor (IGF) are responsible for skin cell hyperproliferation. For paraneoplastic AN, tumoral cells stimulate epidermal growth factor receptor (EGFR) through cytokines such as transforming growth factor-alpha (TGF-alpha) [21]. AN progress from hyperpigmentation to epidermal thickening and accentuation of skin lines. Histologically, it shows hyperkeratosis, mild acanthosis, basilar melanization, and papillomatosis [20].

Regarding management, topical retinoids, keratolytic, topical calcipotriol or chemical peels may be used for cosmetic purposes. However, the primary treatment remains addressing the underlying cause of AN. As a paraneoplastic syndrome, AN is mainly associated with gastrointestinal tumors, especially gastric adenocarcinomas. However, it is important to keep in mind that most cases of AN are associated with benign conditions such as insulin-resistance, obesity, certain medication, or an autosomal dominant mutation. In our case, iatrogenic AN from corticosteroid therapy should be ruled out, while the extensive, symmetrical distribution and the coexistence of tripe palms support a paraneoplastic origin [20, 21].

TP is a very rare paraneoplastic syndrome, often occurring in association with [20]. Clinically, TP is characterized by velvety, hyperkeratotic thickening of the palms (and occasionally soles), and accentuated dermatoglyphics. Regarding histological features and pathogenesis, TP and paraneoplastic AN are similar [19].

Malignant AN and TP tend to resolve with effective cancer treatment and may reappear in cases of recurrence. While both syndromes are primarily associated with lung and gastrointestinal tumors, only a few case reports describe their occurrence in gynecologic malignancies or melanomas [20, 22].

Conclusion

This case highlights several noteworthy aspects: the metachronous occurrence of vaginal melanoma in a patient with a prior history of breast cancer; the simultaneous presence of two paraneoplastic dermatoses (AN and TP); and the additional rare manifestation of DMC. The coexistence of these findings broadens the spectrum of cutaneous paraneoplastic presentations associated with mucosal melanomas and underscores the importance of recognizing dermatologic signs as potential markers of underlying malignancy. It further emphasizes the critical role of a multidisciplinary approach and the need for heightened clinical vigilance in oncologic dermatology. Finally, additional studies are required to elucidate the pathophysiological connections between mucosal melanomas and their cutaneous paraneoplastic expressions.

Authors' contribution

AMS (Writing – original draft; Data curation; Investigation)
OMT (Writing – review & editing; Methodology; Conceptualization)
MEC (Writing – review & editing; Validation; Resources)
LC (Investigation; Validation; Resources)
CADM (Investigation; Validation; Data curation)
AMP (Visualization; Resources; Software)
SHM (Supervision; Validation; Writing – review & editing)

Conflict of interest

None to declare.

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