Radiology Case Reports 19 (2024) 6359–6364

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Primary nipple melanoma in a patient with breast cancer: A diagnosis to consider ☆

Lucia Giudice[a,b], *Sofia Vidali*[b,*], *Pietro Antonini*[c,d], *Elena Nucci*[e], *Federica Di Naro*[b], *Ludovica Anna Incardona*[b], *Vania Vezzosi*[e], *Vincenzo De Giorgi*[f,g], *Jacopo Nori*[b]

[a] *Department of Biomedicine and Prevention, University of Rome "Tor Vergata" viale Oxford 81, 00133 Rome, Italy*
[b] *Breast Radiology Department, Careggi University Hospital, 50139 Florence, Italy*
[c] *Section of Pathology, Department of Diagnostic and Public Health, University of Verona, 37129, Verona, Italy*
[d] *Section of Pathology, Department of Health Sciences, University of Florence, 50121 Florence, Italy*
[e] *Department of Pathology, Careggi University Hospital, 50139 Florence, Italy*
[f] *Section of Dermatology, Department of Health Sciences, University of Florence, 50121 Florence, Italy*
[g] *Cancer Research "Attilia Pofferi" Foundation, 51100 Pistoia, Italy*

ARTICLE INFO

Article history:
Received 13 June 2024
Revised 27 August 2024
Accepted 29 August 2024

Keywords:
Melanoma in situ
Primary malignant melanoma of the breast
Nipple-areola complex pathologies
Nipple-areola complex eczema
Paget's disease
Uncommon nipple malignancy
Ductal carcinoma in situ

ABSTRACT

Melanoma in situ of the nipple is an uncommon diagnosis, with only a few reports in the literature. Due to the variety of pathologies that can affect the nipple-areola complex, the diagnosis can be challenging. In this case report we describe a patient with cosmetic bilateral breast implants who presented with eczema of the left nipple-areola complex and suspicious microcalcifications in the lower inner quadrant of the ipsilateral breast on mammography, subsequently diagnosed with nipple melanoma and concomitant ductal carcinoma in situ.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* Corresponding author.
E-mail address: sofia.vidali@yahoo.it (S. Vidali).

https://doi.org/10.1016/j.radcr.2024.08.156

Introduction

Primary malignant melanoma of the breast (PMMB) is a rare diagnosis, yet nipple melanoma is even less common, accounting for only 0.28-1.8% of all cutaneous melanomas [1]. On initial presentation it is often misdiagnosed as Paget's disease (PD), the most common nipple malignancy. Altogether, the rarity of these NAC pathologies coupled with nonspecific clinical signs and symptoms of disease [2,3], has caused significant delays in diagnosis. To our knowledge, no definitive diagnostic criteria for this group of malignancies has been established to date.

Case presentation

A 43 year-old otherwise asymptomatic female patient was evaluated at the Breast Radiology Department of Careggi University Hospital for 3-week long presentation of eczema of the left NAC. She had previously undergone treatment with topical and systemic antibiotic and steroid therapy without improvement. Her pervious medical and surgical history consisted of bilateral cosmetic breast augmentation, but no further history of previous breast pathology and nor family history of breast cancer. The patient provided informed written consent prior to clinical and diagnostic examinations or treatment.

On clinical examination, the patient reported itching of the left nipple, with no bilateral tenderness or spontaneous discharge. The left nipple appeared erythematous and ulcerated with small peripheral vesicles (Fig. 1). No nipple discharge could be expressed, and no nipple retraction or palpable nodules were noted bilaterally.

Whole breast ultrasound was negative. On mammography, a cluster of fine pleomorphic microcalcifications measuring 12 mm was identified in the inferior inner quadrant of the left breast, classified as BIRADS-4.

Given the presence of suspicious parenchymal features and ipsilateral nipple changes, PD associated with breast cancer was initially suspected. Dermatology consultation for dermoscopy and cutaneous cytology was obtained. Nipple scraping was performed using a semi-automated biopsy gun (Precisa, Hospital Service) with a 14-gauge, 10-cm-long needle placed directly on the dimpled skin: 3 hematopoietic samples were obtained for pathological evaluation. A tomo-guided vacuum-assisted breast biopsy (VABB) was then performed using a vacuum-assisted biopsy device (Mammotome revolve; Devicor Medical Products) with an 8-gauge needle and a commercial mammography system (Selenia Dimension, Hologic, Marlborough, MA). No residual microcalcifications were detected in the examination field on postprocedural imaging, therefore a clip was placed for future localization (Fig. 2).

Contrast-enhanced mammography (CEM) was performed 10 days after VABB on the same mammography system after intravenous injection of iodine-based contrast agent (Iopamire 370 mg mL-1, 1.5 cc/kg actual body weight; Bayer HealthCare, Whippany, NJ) using an automated power injector. This study showed only post-VABB ring enhancement at the biopsy site in the inferomedial quadrant of the left breast.

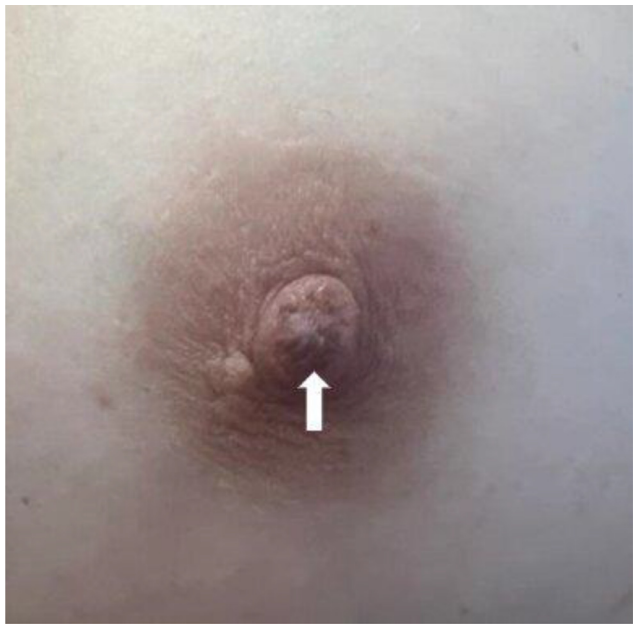

Fig. 1 – Clinical image of the left nipple. Erythema and nipple ulcer with small peripheral vesicles (arrow).

There was no evidence of other suspicious masses or nonmass enhancements (NMEs) (Fig. 3).

The pathological result of VABB sample showed DCIS in the left breast. Molecular characterization by DNA-sequencing showed no mutations in the BRCA1 (NM_007294.4) and BRCA2 (NM_000059.3) genes.

Surprisingly, however, the histologic result of the nipple biopsy documented a proliferation of atypical melanocytes confined within the epidermis, without invasion into the dermis. The melanocytes exhibited cytological atypia, including enlarged nuclei, prominent nucleoli, and irregular nuclear contours. Pagetoid spread of melanocytes along and above the epidermal-dermal junction was observed. Immunohistochemistry revealed positive staining for melanocytic markers such as S100, Mart-1, tyrosinase and HMB-45. All these findings were consistent with a diagnosis of melanoma in situ of the nipple.

Following this diagnosis, the patient underwent a mastectomy resection of the left breast with axillary sentinel lymph node excision. Final histology revealed a pigmented nipple-areola complex lesion, measuring 10 × 8 mm, with features analogous to those observed in nipple biopsy. Immunohistochemical characterization demonstrated expression of S100, MART-1, tyrosinase and polyclonal S100. VE1 (BRAFV600E) was negative. Particular care was paid to distinguishing foci of DCIS in proximity of the epidermis from potential invasive melanoma. The diagnosis of melanoma in situ of the nipple was confirmed (Figs. 4 and 5).

As mentioned above the patient underwent a mastectomy resection of the left breast with axillary sentinel lymph node excision with no surgical early or delayed complications reported.

According to national and international recommendations [4], the patient did not require adjuvant therapy as the lymph

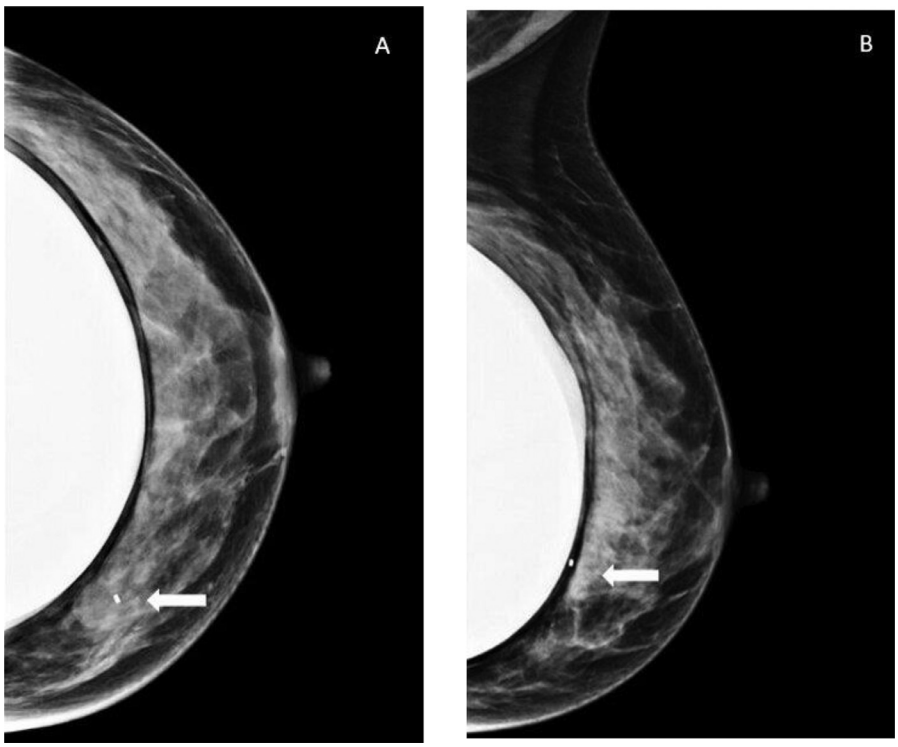

Fig. 2 – Breast mammography after VABB, left breast images. Presence of an oval opacity localized in the inferior inner quadrant of the left breast, referable to post-VABB hematoma, with residual neighboring fine pleomorphic microcalcifications (arrow). (A) cranio-caudal mammogram of the left breast; (B) medial-lateral-oblique mammogram of the left breast.

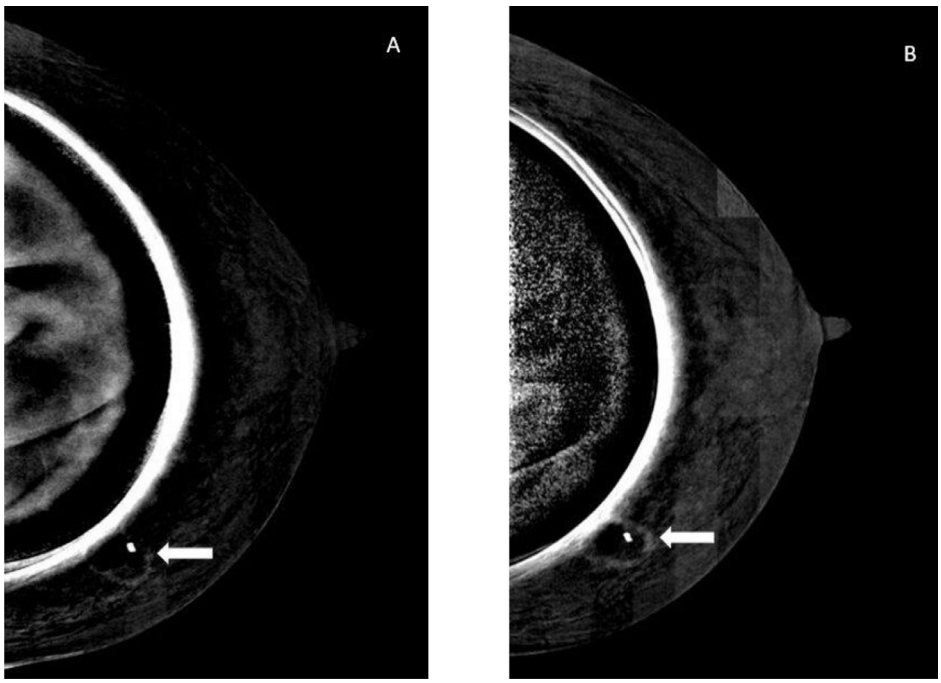

Fig. 3 – Contrast-enhanced mammography (CEM) performed 10 days after VABB, left breast images. Presence of rapid and progressive ring enhancement with contextual metal clip at the site of performed VABB, referable to post-VABB hematoma (arrow). Images partially marred by artifacts due to the presence of breast implants. (A) Cranio-caudal mammogram of the left breast 2 minutes after the injection of iodine-based contrast agent. (B) Cranio-caudal mammogram of the left breast 8 minutes after the injection of iodine-based contrast agent.

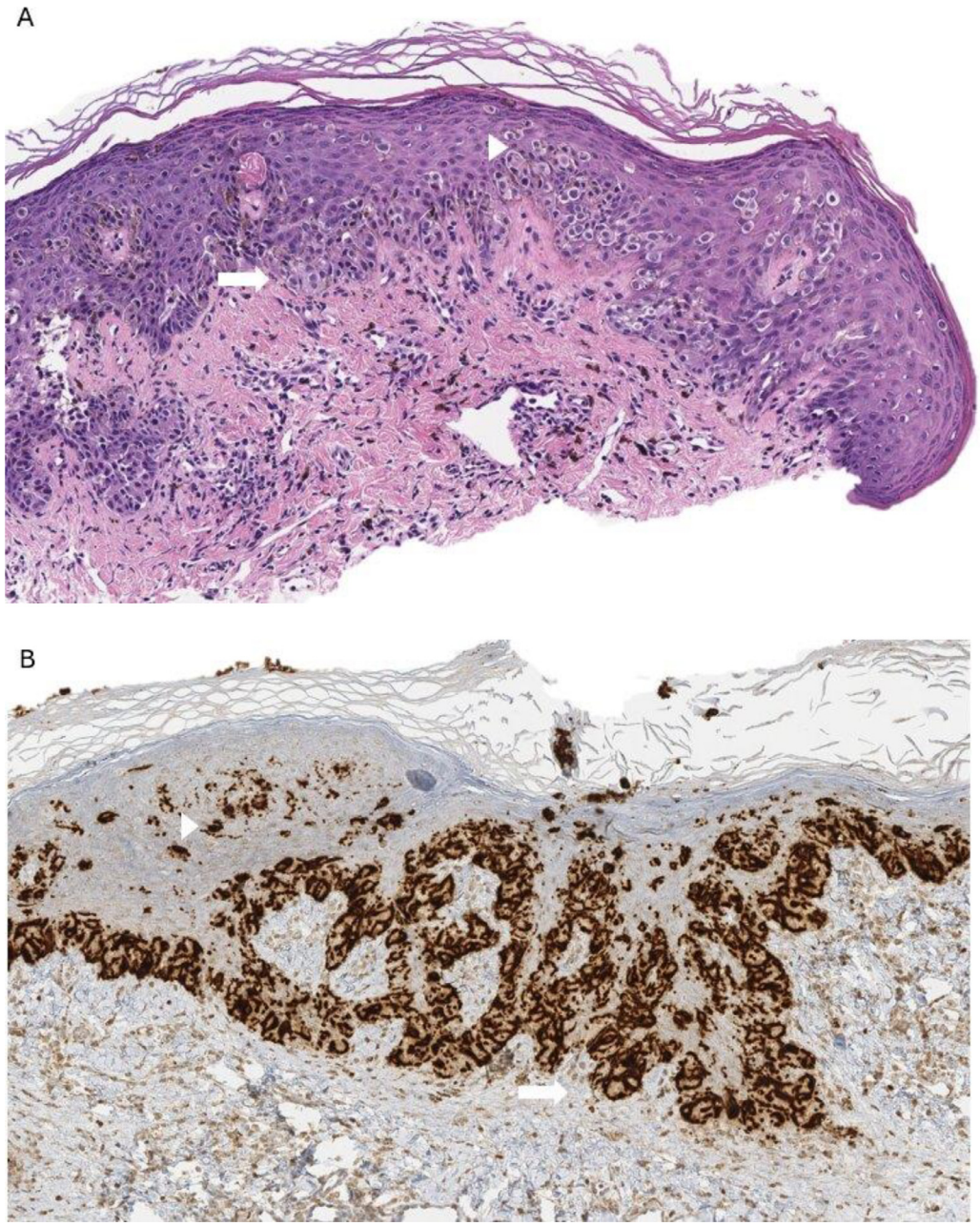

Fig. 4 – Nipple biopsy, histologic images. Proliferation of atypical melanocytes confined to the epidermis, arranged in irregular nests (arrow), and scattered in single elements throughout the epidermal layers. Pagetoid spread (arrowhead) and cytologic atypia are prominent. Invasion into the dermis is absent. (A) Nipple biopsy, Hematoxylin-Eosin (10x); (B) Nipple biopsy, Tyrosinase (10x).

nodes were negative for disease. The patient received indication for annual right mammographic and bilateral US follow-up for 5 years.

Discussion

Breast melanoma is a rare diagnosis and may present with different signs and symptoms. In fact, it can represent a metastatic localization from a cutaneous extra-mammary disease or represent a primary breast lesion (primary malignant melanoma of the breast parenchyma, PMMB). PMMB can also be subclassified into primary cutaneous melanoma, when skin-derived or, less commonly, primary noncutaneous melanoma if glandular-derived [5,6].

Despite being the most common cause of metastases to the breast, metastasis of malignant melanoma and other extra-mammary tumors to the breast is rare, accounting for only 1.3%-2.7% of all breast malignancies. Comparatively, PMMB is even less common, accounting for <0.5% of all breast malignancies [7].

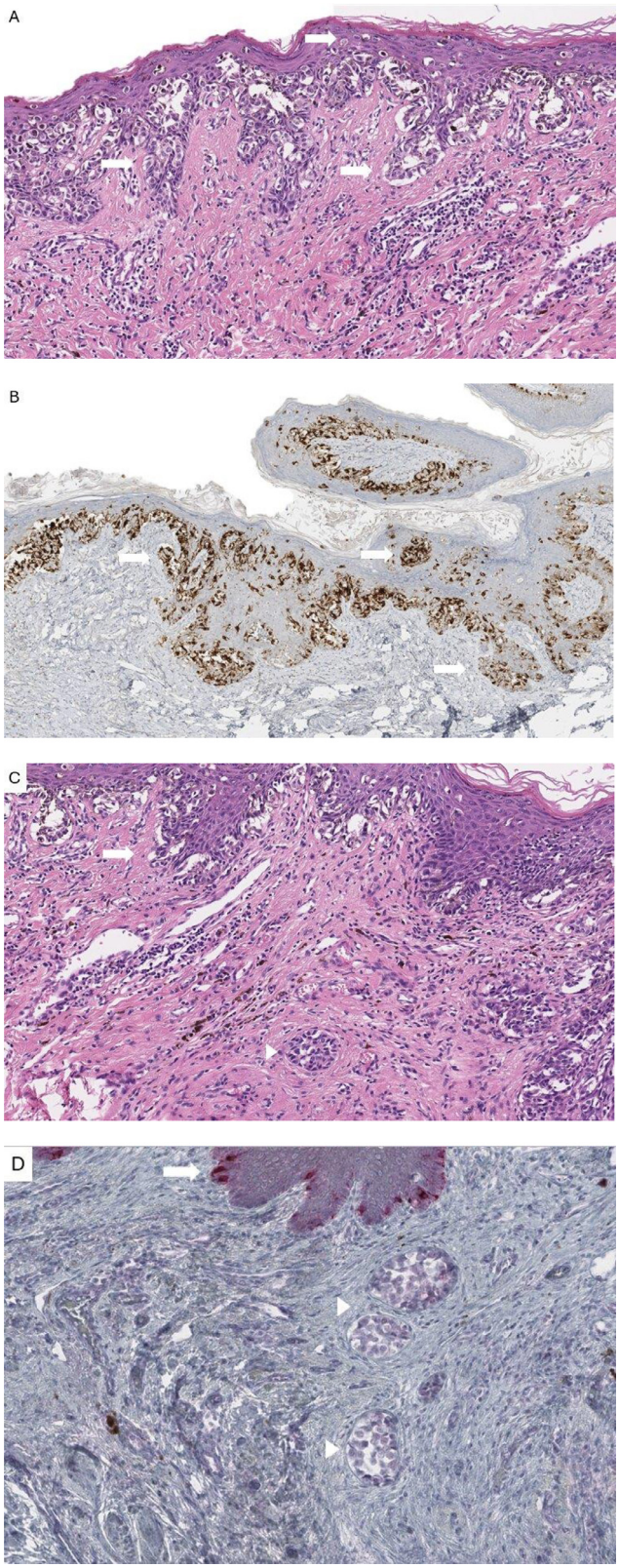

Fig. 5 – Breast specimen, histologic images. Proliferation of atypical melanocytes analogous to that seen in nipple biopsy (arrow). (A) MIS, Hematoxylin-Eosin (10x); (B) MIS, MART-1 (5x); (C) DCIS (arrowhead), Hematoxylin-Eosin (10x); (D) DCIS (arrowhead), tyrosinase (10x).

Diagnosing malignant melanomas of the NAC can be challenging due to specific cutaneous manifestations that may resemble those of other cutaneous malignancies such as PD, metastases, or benign lesions such as nevus, seborrheic keratosis, areolar melanosis and pigmented mammary PD [8–10].

Specifically, PD of the breast is a rare disorder of the NAC that is frequently associated with an underlying cancer. Most cases represent the progression of DCIS to the nipple surface or adjacent skin [2], accounting for 0.5%-5% of all breast carcinomas [11]. Clinical manifestations of PD include eczema, erythema, ulcerated or crusty lesions on the nipple that may spread to the areola, associated with bloody discharge, hyperpigmentation, or retracting of the nipple [12].

Patients often complain pain, itching or burning in the nipple, but they may also be asymptomatic. In most cases, PD is unilateral but contralateral involvement may rarely occur [12].

A rare variant of PD is Pigmented PD, characterized by pagetoid spread of malignant epithelial cells associated with skin pigmentation, making the differential diagnosis with breast malignant melanoma even more doubtful [5].

Although rare, PD is still more frequent than nipple melanoma [8] and therefore it was considered initially as the most probable diagnostic orientation for the here described patient presenting with a highly suspicious cluster of microcalcifications and synchronous erythematous desquamating nipple.

Because of the rarity of PMMB of the nipple, a paucity of literature is available to guide diagnosis of this malignancy. As it has clinical manifestations and symptoms very similar to other diagnostic entities involving NAC such as PD and DCIS. In this patient, presence of microcalcification and a synchronous breast lesion encouraged thorough exploration of the full range of possible diagnoses; however, NAC melanoma should be considered in all cases of abnormal presentation of clinical signs and symptoms resembling these more common malignancies.

Specifically, neoplastic origin should be considered for patients with skin changes and pruritus of the NAC, nipple discharge and other suspicious signs and symptoms, especially if they do not respond to pharmacological therapy. As in the case we present in this report dermatology consultation should be requested ad evaluation obtained [13,14].

Conclusions

In order to increase the body of evidence available for PMMB and to avoid future delays in diagnosis, experiences such as the one we present here should be shared in the scientific literature. We hope that our experience will encourage other clinicians to consider a wide range of possible diagnoses, including PMMB, when evaluating patients with unresolving NAC skin changes to prevent complications of late-stage disease.

Patient consent

We hereby state that for the use of this medical case, details, including imaging studies, photographs, and clinical data, for

the purposes of publication in a medical journal has been done respecting securing anonymization of personal data. This statement ensures that the patient is fully informed about the publication of their case details and consents to the use of their medical information in a way that respects their privacy.

REFERENCES

[1] D'Aiuto G, Del Vecchio S, Mansi L, D'Aprile M, Botti G, Salvatore M. Malignant melanoma of the nipple: a case studied with radiolabeled monoclonal antibody. Tumori 1991;77(5):449–51. doi:10.1177/030089169107700517.

[2] Solinas A, Mahar A, Cooper WA, Thompson JF, Spillane AJ, Scolyer RA. Pigmented Paget's disease of the nipple mistaken for melanoma in situ: a diagnostic pitfall for the unwary. Pathology 2018;50(3):364–7. doi:10.1016/j.pathol.2017.09.018.

[3] Streng A, Gutjahr E, Aulmann S, Flechtenmacher C, Toberer F, Heil J, et al. Pathologie der Mamillenregion: I. Morbus Paget der Mamille, Varianten und Differenzialdiagnosen [Pathology of the nipple-areola complex: I. Paget's disease of the nipple, variants, and differential diagnoses]. Pathologe 2020;41(4):393–9 German. doi:10.1007/s00292-020-00772-1.

[4] Banerjee SS, Harris M. Morphological and immunophenotypic variations in malignant melanoma. Histopathology 2000;36(5):387–402. doi:10.1046/j.1365-2559.2000.00894.x.

[5] Koh J, Lee J, Jung SY, Kang HS, Yun T, Kwon Y. Primary malignant melanoma of the breast: a report of two cases. J Pathol Transl Med 2019;53(2):119–24. doi:10.4132/jptm.2018.10.18.

[6] Drueppel D, Schultheis B, Solass W, Ergonenc H, Tempfer CB. Primary malignant melanoma of the breast: case report and review of the literature. Anticancer Res 2015;35(3):1709–13.

[7] Dang BQ, Miles B, Young P, He J, Nguyen QD. Rare primary malignant melanoma of the breast presenting as a solitary breast mass in a 43-year-old male. Cureus 2023;15(11):e48114. doi:10.7759/cureus.48114.

[8] Dehner CA, Johnson EF, Peters MS, Guo RR. Primary melanoma of the nipple: report of 10 cases including coexistence with Paget's disease. Pathol Res Pract 2024;253:155058. doi:10.1016/j.prp.2023.155058.

[9] Mahmoudzadeh L, Abbasi A, Mahmodlou R, Aghayan S, Asghari R. Malignant melanoma of the nipple with axillary metastasis. JCO Oncol Pract 2020;16(8):516–18. doi:10.1200/JOP.19.00803.

[10] Brugués A, Iranzo P, Díaz A, Peña A, Estrach MT, Carrera C. Pigmented mammary Paget disease mimicking cutaneous malignant melanoma. J Am Acad Dermatol 2015;72(4) e97-8. doi:10.1016/j.jaad.2015.01.015.

[11] Lim HS, Jeong SJ, Lee JS, Park MH, Kim JW, Shin SS, et al. Paget disease of the breast: mammographic, US, and MR imaging findings with pathologic correlation. Radiographics 2011;31(7):1973–87. doi:10.1148/rg.317115070.

[12] Sandoval-Leon AC, Drews-Elger K, Gomez-Fernandez CR, Yepes MM, Lippman ME. Paget's disease of the nipple. Breast Cancer Res Treat 2013;141(1):1–12. doi:10.1007/s10549-013-2661-4.

[13] Tosti G, Salvini C, Barisani A, In Vaccari S. Situ melanoma of the nipple and areola: a dermoscopic report in two new cases. Dermatol Pract Concept 2021;11(2):e2021001. doi:10.5826/dpc.1102a01.

[14] Cinotti E, Galluccio D, Tognetti L, Habougit C, Manganoni AM, Venturini M, et al. Nipple and areola lesions: review of dermoscopy and reflectance confocal microscopy features. J Eur Acad Dermatol Venereol 2019;33(10):1837–46. doi:10.1111/jdv.15727.