Int J Clin Exp Pathol 2022;15(6):253-257
www.ijcep.com /ISSN:1936-2625/IJCEP0142871

*Case Report*

# Nipple adenoma with ipsilateral Spitz nevus in a 26-year-old female: a case report

Xiaofeng Hu[1], Zhongxin Lu[2]

*[1]Jianghan University, Wuhan 430000, China; [2]Department of Clinical Laboratory, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China*

Received March 14, 2022; Accepted April 28, 2022; Epub June 15, 2022; Published June 30, 2022

**Abstract:** A 26-year-old female with a palpable mass and progressively darker itchy area in her left nipple was admitted to hospital. The left nipple surface showed furfuraceous desquamation and bloody discharge, with a 1.0×0.7×0.4 cm area of grayish-brown pigmentation in the ipsilateral nipple and areola. Surgical resection of the primary skin tumor and biopsy of the partial mass in the middle of the nipple were undertaken since color Doppler ultrasonography and dermoscopy were unable to make a differential diagnosis. We thus report the first case of a nipple adenoma with concomitant ipsilateral nipple areola Spitz nevus.

**Keywords:** Nipple adenoma, breast tumor, Spitz nevus, differential diagnosis

## Introduction

Nipple adenoma (NA) was first described by Jones in 1955 as "florid papillomatosis of the nipple" and was defined by the World Health Organization (2012) as a benign epithelial hyperplasia confined to the collecting nipple ducts [1]. It predominates in women aged 40-50 years old, but can also be found in men and children. It has a variety of clinical manifestations, including nipple masses, blood and body fluid production, and ulcers. It can be easily misdiagnosed as malignant lesions, such as Paget's disease or other invasive carcinoma, and thus overtreatment occurs. At the same time, the disease presents simply as a flaking and itchy skin, and can be easily confused with certain skin conditions such as nipple eczema, psoriasis, and dermatitis. While imaging tests such as dermoscopy and ultrasonography or mammography may be helpful, histology is essential to confirm the diagnosis [2, 3].

Spitz nevi consist of pyknotic and/or epithelial cells and most are mixed pigmented nevi. Spitz nevi was found to correlate with prepubertal age and can also be seen in adults. Older age is associated with a progressively higher risk of melanoma-like lesions. The clinical and pathologic features of Spitz nevus can be easily confused with atypical Spitz tumor and Spitzoid melanoma [10-12]. The diagnosis and differential diagnosis mainly depend on clinical manifestations, dermoscopic examination, and biopsy findings.

## Case presentation

A 26-year-old woman was admitted to the central hospital of Wuhan for gradual enlargement of a mass in the left breast for 6 years. The patient had never been treated before. The signed informed consent was obtained. The specialized condition (**Figure 1**) was as follows. Her breasts were symmetrical, and skin pigmentation of 0.5×0.5 cm was at 9 o'clock on the left nipple, whose surface showed furfuraceous desquamation. There was no obvious mass in both of the breasts except the palpable mass in its left nipple. Doppler ultrasonography was performed on the bilateral mammary glands. A slightly strong echogenic area was found at the left mammary papilla, and its nature was uncertain. Preliminary clinical diagnosis revealed a mass on the left nipple. After admission, the patient underwent nipple lesion removal surgery under general anesthesia. On gross examination, there was one small gray-

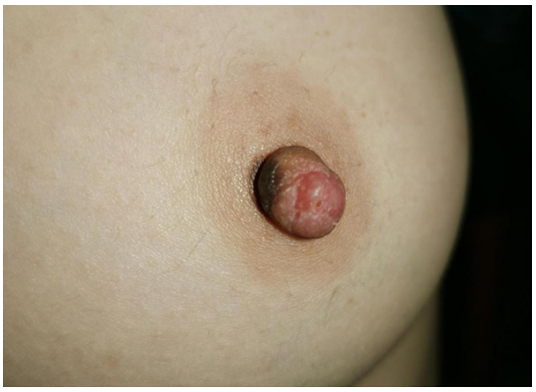

**Figure 1.** A pink nodule is visible on the left nipple, protruding from the surface of the skin. The surface is rough, and borders are clear, with shedding, rupture, and bleeding. Skin pigmentation of 0.5×0.5 cm is at 9 o'clock.

ish-brown tissue with a size of 1.0×0.7×0.4 cm. Microscopic examination showed a nipple adenoma/papillary erosive adenomatosis in the left papillary mass with involved incision margin. In addition, Spitz nevus was associated with active local cell proliferation. Immunohistochemical staining of nevus revealed HMB-45, S-100 (+), P16 (+), CK7 (-), and the Ki-67 hotspot area was about 8%. As with papillary adenoma, ER, CK5/6 (partial glandular epithelium +), P63, and SMA (myoepithelium +) were found (**Figures 2**, **3**). Reexamination of breast ultrasound on April 21, 2020 showed a low echogenic area of the left breast, which was considered as hyperplastic nodules, category 3BI-RADS. No obvious enlarged lymph nodes were found in bilateral axillae. No obvious pigment deposition was found in the sutures of the nipple and areola area after surgery, and the nipple mass was accompanied by prolonged bleeding from the ulcers.

## Discussion

The unique clinical manifestations and pathologic characteristics of nipple adenoma (NA) were first described by Jones in 1955 [1]. In the following decades, with the increasing resolution of electron microscopy, the improvement and widespread use of dermatoscopy technology have helped to diagnose breast tumors as well as skin lesions [2, 3]. As a proliferative process of lactiferous ducts of the nipple, NA accounts for 1% of the incidence of benign breast tumors. It is most common in females aged 40-50 years old, and can also be found in men and children. Clinical manifestations are varied, mostly single, common on the left side, and usually without obvious self-awareness symptoms. Some patients will have symptoms like local nipple mass, erythema, itchiness, pain, or serous or bloody discharge. Histologically, NA can appear similar to mammary Paget's disease and these are often difficult to distinguish. At the same time, it is easily confused with other breast conditions, such as breast ductal cancer, breast duct dilatation, nipple warts, mastofibroma, impetigo, psoriasis, and extragenital syphilis [4, 5]. Mammography, breast ultrasound, magnetic resonance, and biopsy (diagnostic scraping, pathology section, immunohistochemical analysis) are helpful in the diagnosis. Dermotoscopy has received much research attention recently. The characteristic dermatoscopic appearance of NA includes red dots of vascular structures in a linear, radial or semicircular pattern, which helps to differentiate it from other inflammatory or malignant papillary lesions [6]. Based on the histologic changes, the 4 most commonly recognized histologic subtypes of NA are as follows. (1) The papillomatosis type has florid papillary hyperplasia in the epithelial lactiferous duct with occasional mitotic figures. (2) In the sclerosing papillomatosis type, florid papillary hyperplasia with stromal fibers form the structure of ductal lumens, and solid and glandular bodies are found, which causes an illusion of tumor infiltration. (3) The adenosis type shows proliferating glands around hyperplasia, accompanied by obvious hyperplasia of the myoepithelium. (4) The mixed proliferation type may demonstrate features of any of the other three aforementioned subtypes. Histopathologic examination is the gold standard for the diagnosis of papillary adenoma. Histopathologically, NAs are relatively well-defined, non-encapsulated proliferating glands in the dermal matrix of small to medium mammary ducts. The outer layer is covered with cuboidal or squamous myoepithelial cells, and the inner layer is composed of columnar or cylindrical epithelial cells, which together form a double-layered cytoplasmic matrix, also showing apical pulp secretion. The myoepithelial cell layer of the infundibulum can be distinguished by immunohistochemistry using markers of myoepithelial markers such as P63, P40, h-caldesmon, calponin 1, α-smooth muscle protein,

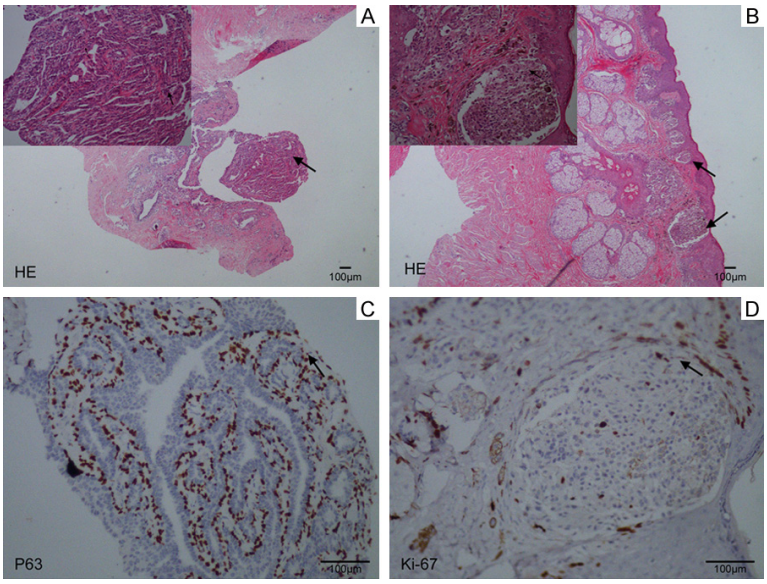


**Figure 2.** Histopathologic findings. A. Nipple adenoma (hematoxylin and eosin stain, ×40, ×200). B. Spitz nevus (hematoxylin and eosin stain, ×40, ×200). C. Nipple adenoma (Immunohistochemically, positive reactivity for P63) (×200). D. Spitz nevus (hotspot area of ki-67 was about 8%) (×200).

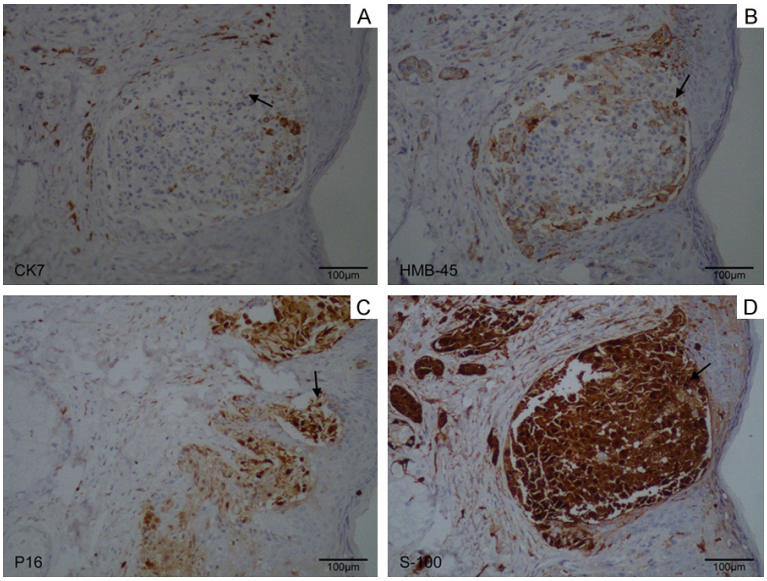


**Figure 3.** Histopathologic findings of Spitz nevus (×200). A. CK7 negative expression. B. Positive expression of HMB-45 in Spitz nevus cytoplasm. C. P16 is positively expressed in the nucleus of nevus cells. D. S-100 has positive expression in the cytoplasm and nucleus in Spitz nevus.

CK5/6, and CD10. Cellular anisotropy is rarely seen. Overlying epithelium displays hyperkeratosis or hypertrophy of the spinous layer. Sclerosis or fibrosis may deform the gland and resemble infiltrative growth. The expression of P63 plays a useful role, since it is negative or expressed discontinuously in breast cancer and helps to distinguish benign papillary adenomas from the invasive carcinomas of the breast [7, 8]. In this study, without early diagnosis and treatment, the nipple's damaged tissue formed a nodular mass, partly protruding from the body surface, with obvious sloughing and ulcer bleeding. Since the patient was unmarried, only a few diseased tissue foci were biopsied, showing prominent tissue deformation, prolonged ulceration, and prolonged bleeding. Surgery is still the most effective way to treat NA. At present, it is common to remove the partial or complete nipple. Nistotomy removal under Mohs-microscope can completely remove part of the function and preserve important parts, which is a psychological hardship for patients [9]. The recurrence after complete resection of the tumor is rare, but for adult women of childbearing age, whether surgery should be performed for NA is still controversial. Selective interventional therapy includes cryotherapy, radiofrequency elimination, and a tendency to retain partially intact tissue, preserving part of the tissue function and aesthetics. Although concurrent cases of NA and ipsilateral or contralateral breast cancer have been reported in the literature, the specific relationship remains unclear to this day. Most scholars believe that patients with NA are less likely to develop breast cancer, but cancer can never be ruled out. Thus, regular follow-up makes sense for NA patients.

Spitz nevus is generally found on the head, neck, and lower extremities, but rarely seen on

the areola. The lesions located in the epidermis and dermis of the skin are called borderline tumor. Lesions are single hard papules, rashes, or nodules, with occasional multiple rashes known as benign melanocytic lesions with or without hyperpigmentation. Lesions are orange, purple-red, reddish brown, dark brown, or black. Spitz nevi are smooth, glabrous, typically less than 8 mm in size, rarely up to 1-2 cm in size, and have their own characteristic driver genes for genomic fusion, rather than activated oncogenes that drive other moles and melanoma [10-12]. Despite a thorough genetic analysis of Spitz nevus, a definitive driver gene for carcinogenesis has not yet been identified. It is difficult to clearly distinguish it from malignant melanoma, spitzoid melanoma, and atypical Spitz tumors in terms of clinical manifestations, dermoscopy, and immunohistochemistry of pathologic tissues. Overdiagnosis of Spitz nevi as melanoma is an ongoing problem. The typical Spitz nevus is usually associated with the presence of a punctate vascular pattern. Dermoscopically, it consists of spots and monomorphic blood vessels that are regularly distributed on a pink background. As the standard for the diagnosis of Spitz nevus, histopathology manifests that the nevus cells are mainly nested in the epidermis and dermis, and their volume decreases with depth. Mitoses are rare. S-100 (+), Melan-A (+), and Mart-1 (+) suggest a pigmented nevus. A low ki-67 index represents a weak proliferative capacity of this nevus cell cycle. P16 (+), and P5 (-) are suggestive of a benign nevus. P5 (-) is particularly regarded as benign. Recently, broad-spectrum MAPK activation changes have been identified in Spitz nevus that differ from other types of melanocytic nevi [13-15].

Larger samples are needed for study. The disease is mostly surgically removed, and if the pathologic changes are suspected to be malignant, complete resection should be performed with long-term postoperative follow-up to observe for recurrence [16].

## Conclusion

To our knowledge, ours is the first reported case with concomitant nipple adenoma and Spitz nevus of the areola. With the emphasis on breast self-examination and the development of ultrasound technology, breast diseases are detected, diagnosed, and treated earlier. Spitz nevus is a benign tumor, but in this case, the lesion was located in a highly frictional area and the skin pigmentation was growing year by year, suggesting a risk of malignant transformation. Because the patient had not yet given birth, the intact NA tissue was not removed during surgery to preserve partial tissue, and the erosion surface continued to decompose and bleed, which was inconvenient to the patient. We recommend surgical treatment after childbirth. This paper aims to raise awareness of these two conditions, which occur rarely in adults and require prompt diagnosis and treatment.

## Acknowledgements

The author would like to thank all medical staff who were involved in this remarkable patient's diagnosis and nursing care. Most importantly, they would thank the patient for allowing them to share her story to educate others.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Zhongxin Lu, Department of Clinical Laboratory, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China. Tel: +86-15827518691; E-mail: LZX71@yahoo.com

## References

[1] Jones DB. Florid papillomatosis of the nipple ducts. Cancer 1955; 8: 315-319.
[2] Ansari MS, Taghizadeh Fazli J and Ehsani A. Dermoscopy of nipple adenoma. Clin Case Rep 2020; 8: 3254-3256.
[3] Lyons D, Wahab RA, Vijapura C and Mahoney MC. The nipple-areolar complex: comprehensive imaging review. Clin Radiol 2021; 76: 172-184.
[4] Raivoherivony ZI, Feron J and Klijanienko J. The utility of nipple scraping in the diagnosis of paget disease of the breast. Diagn Cytopathol 2019; 47: 249-250.
[5] Liu XK and Li J. Erosive patches on bilateral nipples. JAMA Dermatol 2018; 154: 719-720.
[6] Tasdelen I and Soylu Boy FN. Florid papillomatosis of the nipple. Breast J 2020; 26: 1849-1850.

[7] Azzopardi JG and Salm R. Ductal adenoma of the breast: a lesion which can mimic carcinoma. J Pathol 1984; 144: 15-23.
[8] Errichetti E, Avellini C, Pegolo E and De Francesco V. Dermoscopy as a supportive instrument in the early recognition of erosive adenomatosis of the nipple and mammary paget's disease. Ann Dermatol 2017; 29: 365-367.
[9] Owen JL and Krunic AL. Successful treatment of nipple adenoma using mohs micrographic surgery to preserve the nipple-areolar complex. Dermatol Surg 2020; 46: 132-135.
[10] Crignis GS, Abreu LD, Buçard AM and Barcaui CB. Polarized dermoscopy of mammary Paget disease. An Bras Dermatol 2013; 88: 290-292.
[11] Harms KL, Lowe L, Fullen DR and Harms PW. Atypical spitz tumors: a diagnostic challenge. Arch Pathol Lab Med 2015; 139: 1263-1270.
[12] Raghavan SS, Peternel S, Mully TW, North JP, Pincus LB, LeBoit PE, McCalmont TH, Bastian BC and Yeh I. Spitz melanoma is a distinct subset of spitzoid melanoma. Mod Pathol 2020; 33: 1122-1134.
[13] Elder DE and Barnhill RL. The pink papules and plaques of Spitz. Br J Dermatol 2019; 181: 235.
[14] Ferrara G, Gianotti R, Cavicchini S, Salviato T, Zalaudek I and Argenziano G. Spitz nevus, Spitz tumor, and spitzoid melanoma: a comprehensive clinicopathologic overview. Dermatol Clin 2013; 31: 589-598.
[15] Raghavan SS, Kapler ES, Dinges MM, Bastian BC and Yeh I. Eruptive Spitz nevus, a striking example of benign metastasis. Sci Rep 2020; 10: 16216.
[16] Sainz-Gaspar L, Sanchez-Bernal J, Noguera-Morel L, Hernandez-Martin A, Colmenero I and Torrelo A. Spitz nevus and other spitzoid tumors in children. Part 2: cytogenetic and molecular features. Prognosis and treatment. Actas Dermosifiliogr (Engl Ed) 2020; 111: 20-25.