Case report

Sebaceous vs. lipid-rich carcinoma of the breast. Clinicopathological characteristics and correlations – a report of two cases and a literature review

Nikola Živković[1], Ana Cvetanović[2], Miloš Kostić[3], Maja Jovičić Milentijević[1], Miodrag Djordjević[4], Tijana Denčić[1], Julija Cvetković[1], Mirjana Ćuk[5]

[1]Department of Pathology, Faculty of Medicine Niš, University of Niš, Serbia
[2]Department of Oncology, Faculty of Medicine Niš, University of Niš, Serbia
[3]Department of Microbiology and Immunology, Faculty of Medicine Niš, University of Niš, Serbia
[4]Department of Surgery, Faculty of Medicine Niš, University of Niš, Serbia
[5]Department of Pathology, Faculty of Medicine Foča, University of East Sarajevo, Republic of Srpska, Bosnia and Herzegovina

Primary sebaceous and lipid-rich carcinomas are extremely rare. Sebaceous carcinoma cells are large and oval with light, partially vacuolated cytoplasm. The second population consists of cells located mainly on the peripheral parts of tumour beaches. Those cells are of smaller calibre and are fusiform in appearance. Lipid-rich carcinoma is made up of multiple cell populations. The predominant cell type is with a distinctly light, vacuolated, and partially optically clear cytoplasm. Pathohistological analysis may be overlapping. On one side there is a tumour with a relatively excellent prognosis, and on the other, a highly aggressive carcinoma with a tendency for early metastases.

Key words: breast, immunohistochemistry, lipid-rich carcinoma, sebaceous carcinoma.

Introduction

Primary sebaceous invasive carcinoma is an extremely rare disease of the breast. To date, just over 10 cases have been reported worldwide, with the highest frequency in China with 6 reported cases [1]. The World Health Organisation (WHO) has described this type of neoplasm as sebaceous breast carcinoma based on sebaceous differentiation in over 50% of the neoplastic cell population, in the absence of evidence on the skin adnexa origin [2]. It was first described by van Bogaert and Madalgue in 1977 as a morphological variant of carcinoma that produces fat [3]. However, the first case was presented by Mazzella *et al*. in 1995 under the current entity [4]. Furthermore, micromorphologically very similar lipid-rich carcinoma is also a rather rare primary neoplasm of the breast. The frequency is estimated to be less than 1% regarding all carcinomas of this localisation [5]. Aboumrad *et al*. described lipid-producing carcinoma of the breast, whereas Ramos and Taylor studied it in detail and gave it a formal name [6, 7]. It is described as a neoplasm that contains fat in the cytoplasm of neoplastic cells in the form of vacuoles or a foamy mass. The content is histochemically positive to neutral fats. Histopathologically, these are high-grade tumours with a high degree of polymorphism, extremely poor differentiation, and a high mitotic index [8]. Glandular structures and papillary growth patterns are not observed.

Considering the broad histopathological presentation of breast carcinomas, as well as their high mor-

bidity and mortality, we present 2 rare entities for pathohistological differential diagnosis. Sebaceous and lipid-rich breast carcinomas may have an overlapping micromorphological presentation. Therefore, we have provided a comparative pathohistological and immunohistochemical analysis in correlation with the clinical picture.

Cases reports

The 74-year-old woman presented with a palpable mass in the upper-outer quadrant of the left breast. Mammography showed a circumscribed neoplastic mass, classified as Breast Imaging-Reporting and Data System (BI-RADS) grade 4c. After radiological diagnosis, a tumourectomy was performed. A fragment of fatty and glandular breast tissue 50 mm in diameter with part of the associated skin tissue was submitted for pathohistological evaluation. Macroscopically, a white-grey neoplastic mass of medium-hard consistency and 30 mm in size was observed on the section. The distance from the nearest resection margin was 10 mm, without skin contact. The micromorphological analysis determined that the neoplasm was made up of 2 types of cell populations. The cells were predominantly in lobular arrangements, sometimes forming pseudo-glandular structures. The dominant cell type was sebaceous in appearance – large, oval cells with light and foamy, partially vacuolated cytoplasm. The nuclei of tumour cells were pushed towards the periphery of the cells, with distinct polymorphism. Mitotic figures were pronounced. The second population consisted of cells located mainly on the periphery of the islands of cancer cells. These cells are smaller and fusiform in appearance, with eosinophilic cytoplasm and elongated and hyperchromic nuclei. The tumour had pushing borders. Lymphovascular and perineural invasion were not observed. A desmoplastic stromal reaction was present with a moderate mononuclear leukocyte infiltrate. Necrotic areas were observed focally. Histopathological examination revealed sebaceous breast carcinoma, Nottingham score 8 (nuclear grade 3, histologic grade 3, mitotic grade 2). Immunohistochemical analysis showed that neoplastic cells were positive to oestrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), epithelial membrane antigen, E-cadherin, Cluster of Differentiation 15, also known as Lewis × (CD15), GATA3, post-meiotic segregation increased 2 (PMS2), MutL protein homologue 1 (MLH1), MutS homologue 2 (MSH2), MutS homologue 6 (MSH6), (Figs. 1, 2), and negative to Human Epidermal growth factor receptor 2 (HER2), carcinoembryonic antigen, tumour protein 63 (p63), MAMMAGLOBIN, melan-A, and human melanoma black 45. The Kiel 67 (Ki-67) proliferative index was about 32%. Subsequently, a radical mastectomy was performed without residual carcinoma in the breast tissue. In none of the 28 isolated axillary lymph nodes was a secondary deposit observed. The pathological staging was pT2 pN0. The woman was prescribed hormone therapy, and she regularly reports for check-ups. Fifty-five months have passed since the intervention, with no recurrence or distant metastases.

At the time of the diagnosis of lipid-rich breast carcinoma, the patient was 38 years old. Mammographic analysis confirmed a neoplastic mass in the upper-outer quadrant of the left breast and classified it as BI-RADS grade 4B. The lesion was 25 × 22 × 20 mm in size. First, a core needle biopsy was performed, followed by a tumourectomy. An oval sample of fatty and glandular breast tissue of about 65 mm in diameter was sent for pathohistological analysis. The associated skin sample was also submitted. A white-yellow swelling with indistinctly borders and 25 mm in diameter could be seen on the incision. Tumour consistency was medium-firm. The distance from the nearest surgical resection margin was about 10 mm, without involving the skin. The micromorphological analysis confirmed a neoplastic mass with infiltrative edges, made up of multiple cell populations. The predominant cells were relatively large, with a distinctly light, vacuolated, and partially optically clear cytoplasm. The nuclei were large, pleomorphic, with prominent nucleoli. The islands of cancer cells were irregular in shape, in places with the dissipation of individual cells. Ductal carcinoma *in situ* (solid type, high nuclear grade; NG3) could be seen in the surrounding area. Necrotic areas were extensive, and a desmoplastic stromal reaction was scarce with mild to moderate mononuclear leukocyte infiltrate. Lymphovascular and perineural invasion were observed. Histopathological examination revealed lipid-rich carcinoma of the breast, Nottingham score 8 (nuclear grade 3, histologic grade 3, mitotic grade 2) (Fig. 3). Immunohistochemical analysis suggested that neoplastic cells were positive to cytokeratin 7, E-cadherin, adipophilin, and tumour protein 53 (p53) and negative to ER, PR, AR, HER2, p63, cytokeratin 5/6 (CK5/6), and cytokeratin 14 (CK14). The Ki-67 proliferative index was about 55%. After the applied chemotherapy (fluorouracil, epirubicin and cyclophosphamide [FEC protocol], and Taxotere), a radical mastectomy was performed. Ductal carcinoma *in situ* foci were found in the breast tissue, with no secondary deposits in 24 isolated axillary lymph nodes. The pathologic staging was ypT2 pN0. Thirty-three months after the diagnosis, local recurrence of the disease was pathohistologically confirmed. Certain changes in the lungs that correspond to lung metastases could be seen on the MSCT thorax. The patient was prescribed 10 Capetral cycles. Her state is currently being monitored.

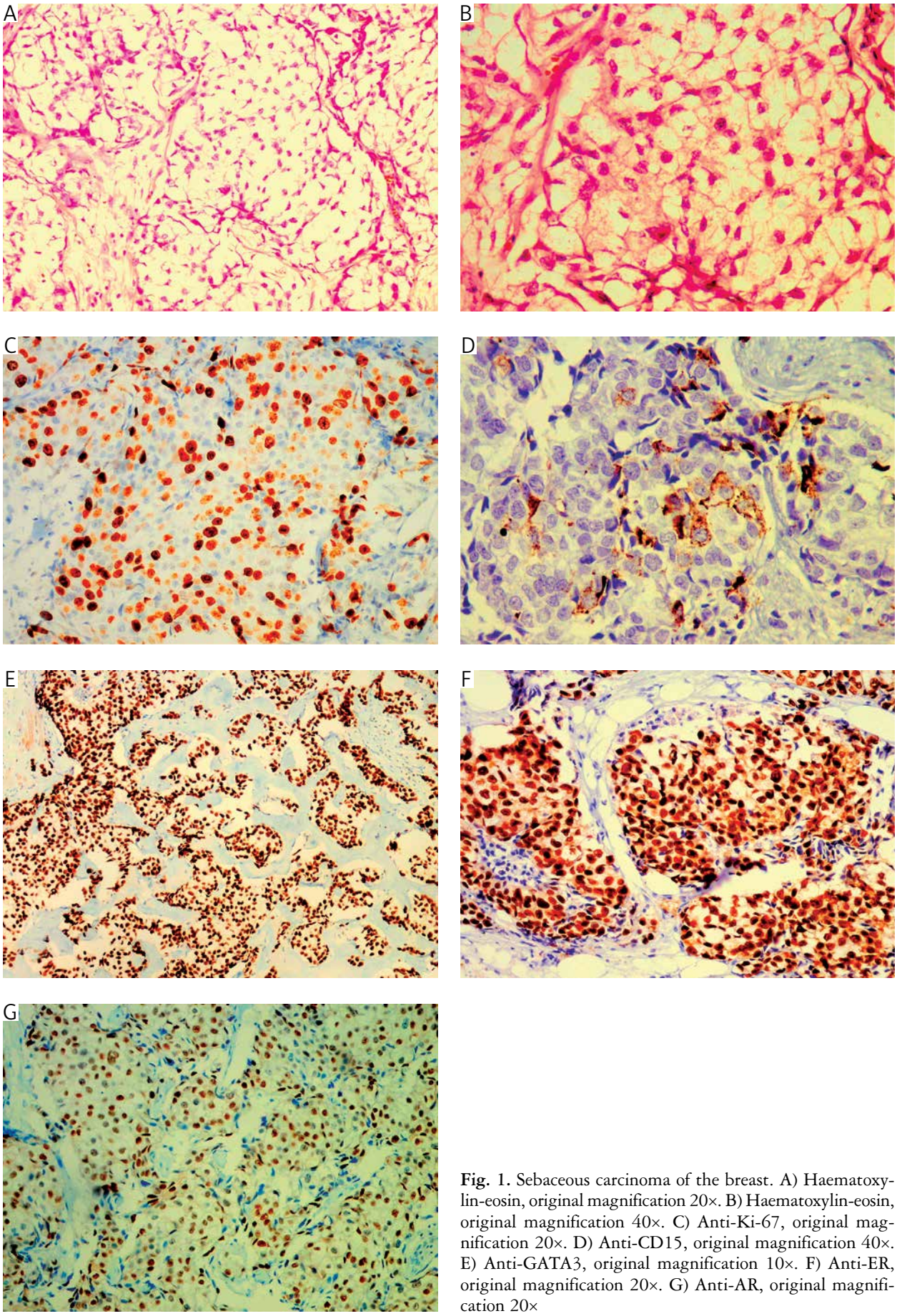

Fig. 1. Sebaceous carcinoma of the breast. A) Haematoxylin-eosin, original magnification 20×. B) Haematoxylin-eosin, original magnification 40×. C) Anti-Ki-67, original magnification 20×. D) Anti-CD15, original magnification 40×. E) Anti-GATA3, original magnification 10×. F) Anti-ER, original magnification 20×. G) Anti-AR, original magnification 20×

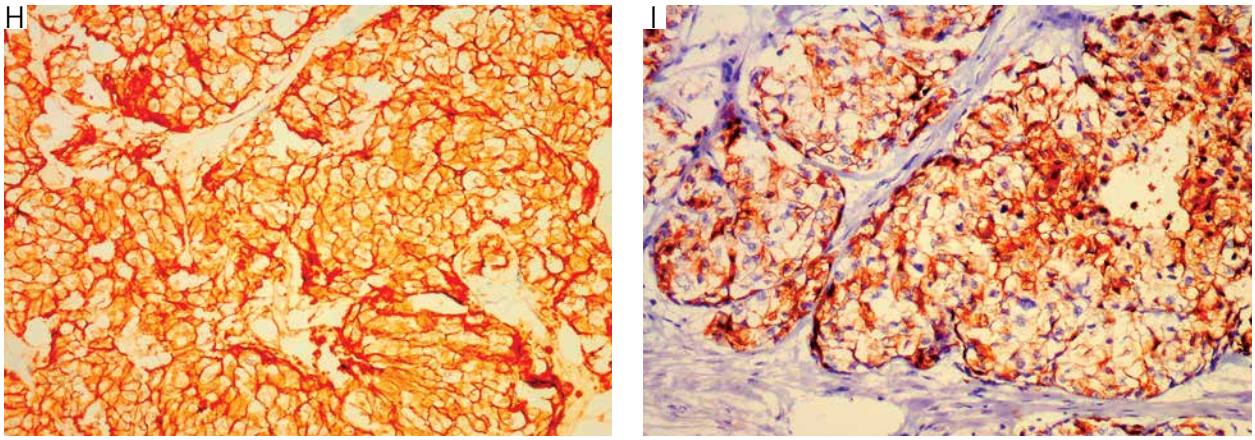

Fig. 1. Cont. H) Anti-E-Cadherin, original magnification 20×. I) Anti- epithelial membrane antigen, original magnification 20×

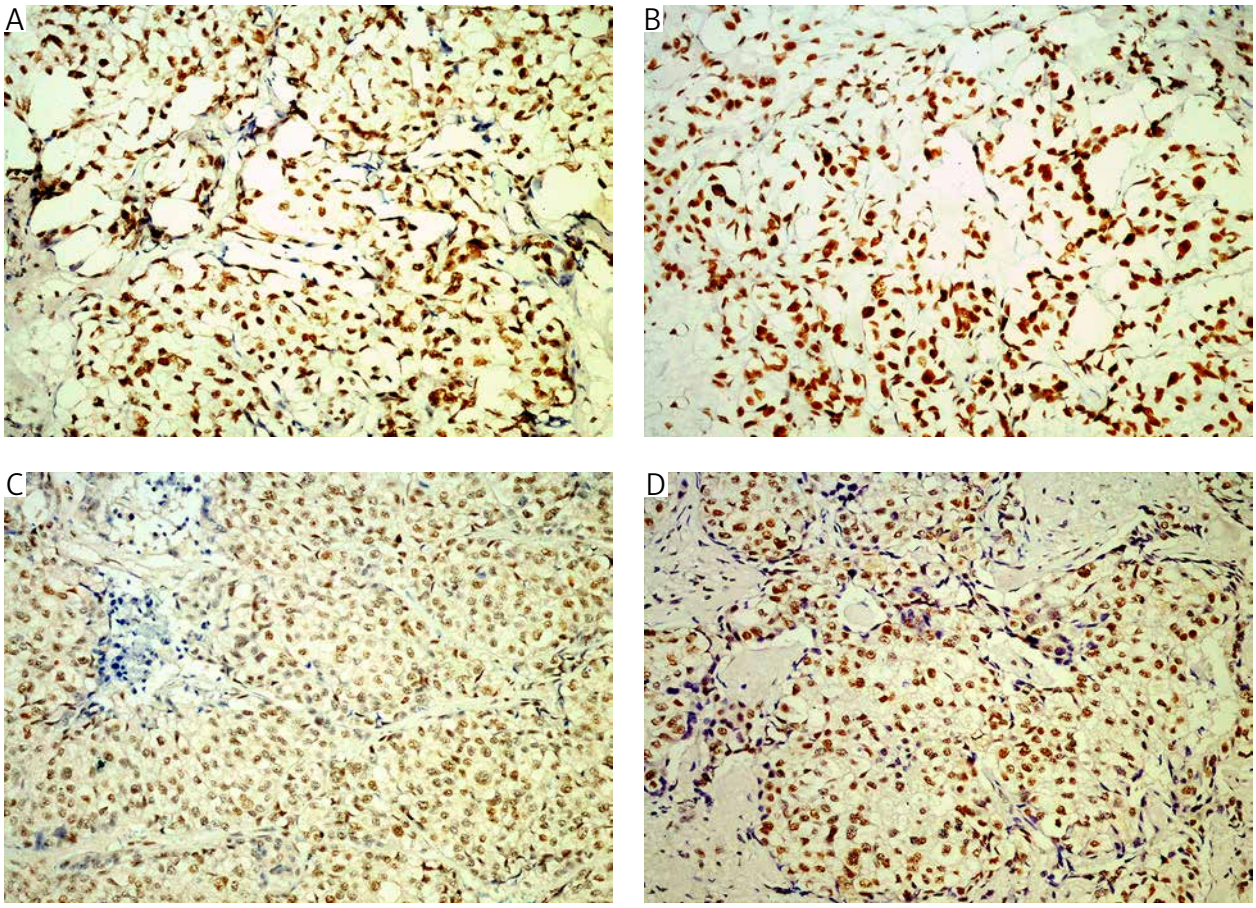

Fig. 2. Sebaceous carcinoma of the breast. A) Anti-MutS homolog 2, original magnification 20×. B) Anti-MutS homologue 6, original magnification 20×. C) Anti-post-meiotic segregation increased 2, original magnification 20×. D) Anti-MutL protein homologue 1, original magnification 20×

Discussion

Primary sebaceous carcinoma of the breast is seldom encountered, given that it is identical to primary sebaceous carcinoma of the skin. The latest WHO classification describes predominant sebaceous differentiation, unlike the previous one, which included more than 50% of cells with this pattern, without evidence on skin origin [2, 9]. Pathohistologically, sebaceous cells form lobular arrangements. Their cytoplasm is abundant, with a smaller or larger number of vacuoles. These cells are surrounded by oval to spindle-shaped cells, with markedly eosinophilic cytoplasm, without vacuolisation. The nuclei of se-

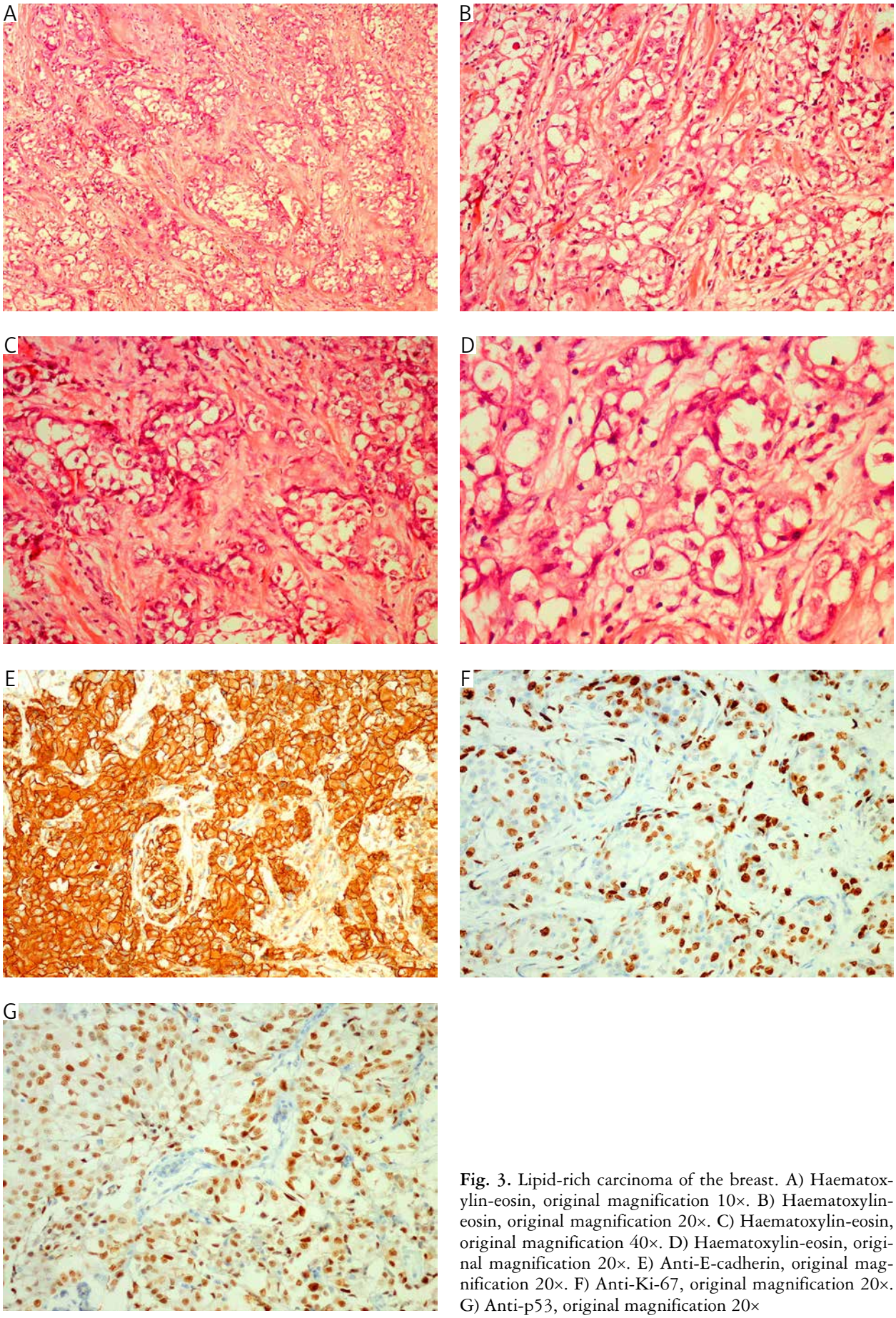

Fig. 3. Lipid-rich carcinoma of the breast. A) Haematoxylin-eosin, original magnification 10×. B) Haematoxylin-eosin, original magnification 20×. C) Haematoxylin-eosin, original magnification 40×. D) Haematoxylin-eosin, original magnification 20×. E) Anti-E-cadherin, original magnification 20×. F) Anti-Ki-67, original magnification 20×. G) Anti-p53, original magnification 20×

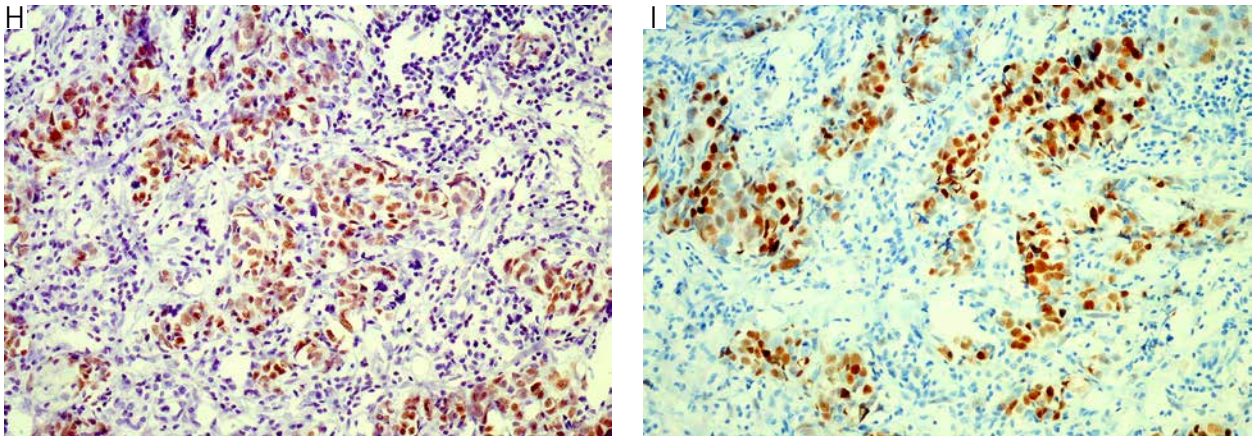

Fig. 3. Cont. H) Anti-GATA3, original magnification 20×. I) Anti-AR, original magnification 20×

baceous cells are eccentrically positioned and express a moderate to extremely high degree of pleomorphism. In our cases, we had neoplasms of grade 3 [10]. The distinction between a primary skin origin can only be made when there is no contact with the skin or when the neoplasm is surrounded by normal breast tissue [11, 12]. The histogenesis of this neoplasm in the breast is still vague. It is assumed that these are reserve ductal cells capable of sebaceous differentiation, as well as the reposition of the embryonic group of epidermal cells into the breast tissue [13, 14]. The analysis of the cases described so far shows that the age varies in the range 25–85 years, with a total of 3 cases of male breast cancer described. The analysis of steroid receptors and the expression of the HER2 oncoprotein suggested that the luminal subtype is the most common type of carcinoma. However, cases of triple-negative carcinoma have also been recorded. Our patient was diagnosed with a hormone-dependent and HER2-negative carcinoma, excluding regional or distant metastases. The analysis of GATA3, mammaglobin, and gross cystic disease fluid protein 15 further confirmed the primary origin of the breast, i.e. the positive expression of CD15 confirmed sebaceous differentiation [15, 16].

Lynch syndrome is caused by a mutation in the mismatch repair (MMR) genes, leading to microsatellite instability. This syndrome predisposes to malignancy. Using immunohistochemical staining, mutations in MMR can be detected as loss of nuclear expression in *PMS2*, *MLH1*, *MSH2*, and *MSH6* within the tumour. Muir-Torre syndrome is a variant of Lynch syndrome. According to the literature, there has been no loss of MMR expression observed in invasive breast sebaceous carcinoma [17]. Immunohistochemical analysis of the expression of PMS2, MLH1, MSH2, and MSH6 proteins was performed, and their positive reaction ruled out Muir-Torres syndrome [12, 14]. In this way, the potential existence of visceral metastases can be ruled out, which has been confirmed by clinical monitoring so far.

To date, lipid-rich carcinoma of the breast has been described in only a few studies, as a series of cases or individual reports. These are highly aggressive carcinomas with a low survival rate. The precise definition remains a major controversy regarding the number of neoplastic cells possessing fat vacuoles. Certain studies suggest that the presence of fat vacuoles is required in over 90% of neoplastic cells [18]. The differential diagnosis may include glycogen-rich carcinoma, apocrine, sebaceous, and secretory carcinoma of the breast, but also metastases of clear cell carcinoma of the breast [19, 20]. It is most often localised in the upper-outer quadrant, equally in both breasts, in the form of a lobular mass. Pathohistologically, neoplastic cells are polygonal in shape with abundant, vacuolated or foamy cytoplasm. Their nuclei are pleomorphic, with dispersed chromatin and prominent nucleoli. The islands of cancer cells have an oval or strip arrangement. Moreover, the cells may have an alveolar arrangement, with a high degree of cellular polymorphism, and oncocytic or apocrine presentation.

Basic micromorphological parameters of sebaceous and lipid-rich breast carcinoma are provided in Table I.

A specific immunohistochemical profile of neoplastic cells does not exist. Most often, we are dealing with neoplasms negative to steroid hormones, CK5/6, CK14, tumour protein 40 (p40), and S100, but also HER2 positive expression in about 70% of cases [5, 21, 22]. In our case, it is a triple negative carcinoma with a Ki-67 proliferative index of about 55%. The origin of cytoplasmic fat causes great controversy. It is known that normal ductal epithelial cells can synthesise glycogen, carbohydrates, and lipids. The ultrastructural analysis of cancer cells found that fat in the cytoplasm is not a product of degenerative processes. Studies have proven that it is a matter of the accumulation of fats with a membrane. They are located mostly near the Golgi apparatus and enlarged endoplasmic reticulum [7, 23]. Guided

Table I. Histopathological characteristics of sebaceous and lipid-rich breast carcinoma

Characteristics	Sebaceous carcinoma of the breast	Lipid-rich carcinoma of the breast
Cell types	2 types	More than 2 types
Cytoplasm	Vacuolated	Vacuolated, rich in fats
Cellular arrangement	Lobular	Irregular
Mitoses	Moderate	Moderate to high
DCIS	Absent	Present
Neoplastic borders	Pushing	Infiltrative
ER/PR	+/+	–/–
Ki-67 proliferative index	High, up to 50%	High, over 50%

DCIS – ductal carcinoma in situ, ER – oestrogen receptor, PR – progesterone receptor

Table II. Clinicopathological and immunohistochemical characteristics of sebaceous and lipid-rich breast carcinoma

Parameters	pT1	pT2	pT3	Lymph nodes metastasis	HR+	HER2+	Ki-67 < 20%	Ki-67 > 20%
Sebaceous carcinoma	11/23	11/23	1/23	9/23	16/23	2/23	6/23	13/23
Lipid-rich carcinoma	38/82	42/82	2/82	42/82	41/46	26/46	8/46	19/46

HR+ – hormone dependent, HER2+ – HER2 positive expression, pT1 – tumour size up to 2 cm, pT2 – tumour size 2–5 cm, pT3 – tumour size greater than 5 cm

by the most significant and available data from the literature, primarily from larger studies, Table II shows significant clinicopathological and immunohistochemical characteristics of sebaceous and lipid-rich breast carcinoma [5, 14, 24].

Russo *et al*. presented a case of lipid-rich carcinoma with a basal-like phenotype, initially without distant metastases, whereas Reis-Filho *et al*. presented a case of a patient with prolactin positive triple-negative lipid-rich carcinoma [25, 26]. This study is distinguished by the fact that neoplastic cells were positive to S100 protein; thus, they recommended this antibody as a marker in the differential diagnosis of lipid-rich carcinoma. The patient's follow-up revealed a stable disease for 20 years. A case of lipid-rich carcinoma with an atypical histopathological and clinical picture reported by Gaspar *et al*. has attracted special attention [27]. It involves a patient with grade 1 carcinoma, completely hormone-dependent, HER2-negative carcinoma with a Ki-67 proliferative index of less than 1%. A relapse of the disease occurred 18 months after chemotherapy. At that time, both visceral and nodal metastases were noted. The prescribed chemotherapy proved to have an excellent response.

Conclusions

Early, accurate, and precise pathohistological diagnosis has a key impact on the survival rate and clinical follow-up of each patient. Considering the enormous breadth of the micromorphological presentation using a different immunohistochemical analysis, these 2 entities deserve special attention. Pathohistological analysis may be overlapping, potentially leading to misdiagnosis. On the one hand, we have a tumour with a relatively excellent prognosis, and on the other, a very aggressive carcinoma with a high propensity for early metastases, disease relapses, and recurrences, as well as a low survival rate. From the therapeutic point of view, exact guidelines do not exist due to a relatively small sample. To date, combined chemotherapy with radiation, following a radical surgical intervention, has provided the best results, as well as hormonal therapy in cases with proven dependence on steroid hormones, but with a limited effect.

Disclosures

1. This paper was supported by the Ministry of Education and Science of the Republic of Serbia under the project number 41017 (contract number: 451-03-65/2024-03/200113).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

References

1. Heng C, Wei T, Yingbing T, Hanzhong L. Clinicopathological characteristics of breast sebaceous adenocarcinoma. Pol J Pathol 2018; 69: 226-233.
2. Eusebi V, Ichihara S, Vincent-Salomon A, Sneige N, Sapino A. Exceptionally rare types and variants. In: Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ (eds.). WHO classification of tumours of the breast. 4th ed. IARC, Lyon 2012, 71-76.
3. Van Bogaert LJ, Maldague P. Histologic variants of lipidsecreting carcinoma of the breast. Virchows Arch A Pathol Anat Histol 1977; 375: 345-353.

4. Mazzella FM, Sieber SC, Braza F. Ductal carcinoma of male breast with prominent lipid-rich component. Pathology 1995; 27: 280-283.
5. Guan B, Wang H, Cao S, et al. Lipid-rich carcinoma of the breast clinicopathologic analysis of 17 cases. Ann Diagn Pathol 2011; 15: 225-232.
6. Aboumrad MH, Horn Jr RC, Fine G. Lipid-secreting mammary carcinoma. Report of a case associated with Paget's disease of the nipple. Cancer 1963; 16: 521-525.
7. Ramos CV, Taylor HB. Lipid-rich carcinoma of the breast. A clinicopathologic analysis of 13 examples. Cancer 1974; 33: 812-819.
8. Szpor J, Witczak K, Storman M, et al. Breast carcinoma grading on core needle biopsy – to grade or not to grade? Pol J Pathol 2023; 74: 203-210.
9. WHO Classification of Tumours Editorial Board. Breast tumours. 5th ed. IARC Publications, Lyon 2019.
10. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957; 11: 359-377.
11. Švajdler M, Baník P, Poliaková K, et al. Sebaceous carcinoma of the breast: report of four cases and review of the literature. Pol J Pathol 2015; 66: 142-148.
12. Kazakov DV, Spagnolo DV, Kacerovska D, Rychly B, Michal M. Cutaneous type adnexal tumors outside the skin. Am J Dermatopathol 2011; 33: 303-315.
13. Varga Z, Kolb SA, Flury R, Burkhard R, Caduff R. Sebaceous carcinoma of the breast. Pathol Int 2000; 50: 63-66.
14. De Alencar NN, Souza DA, Lourenço AA, Silva RR. Sebaceous breast carcinoma. Autops Case Rep 2022; 12: e2021365.
15. Rutten A, Wick MR, Sangueza OP, Wallace C. Tumours with sebaceous differentiation. In: World Health Organization, editor. WHO classification of tumours. IARC Press, Lyon 2006, 160-163.
16. Ribero S, Baduel ES, Brizio M, et al. Metastatic sebaceous cell carcinoma, review of the literature and use of electrochemotherapy as possible new treatment modality. Radiol Oncol 2016; 50: 308-312.
17. Alvarez Moreno JC, He J. Invasive breast carcinoma with sebaceous morphologic pattern showing lymph node macrometastasis: a case report. Cureus 2023; 15: e37365.
18. Moritani S, Ichihara S, Hasegawa M, et al. Intracytoplasmic lipid accumulation in apocrine carcinoma of the breast evaluated with adipophilin immunoreactivity: a possible link between apocrine carcinoma and lipid-rich carcinoma. Am J Surg Pathol 2011; 35: 861-867.
19. Umekita Y, Yoshida A, Sagara Y, Yoshida H. Lipid-secreting carcinoma of the breast: a case report and review of the literature. Breast Cancer 1998; 5: 171-173.
20. Kurisu Y, Tsuji M, Shibayama Y, Takahashi Y, Nohara T. Intraductal lipid-rich carcinoma of the breast with a component of glycogen-rich carcinoma. J Breast Cancer 2012; 15: 135-138.
21. Shi P, Wang M, Zhang Q, Sun J. Lipid-rich carcinoma of the breast: a clinicopathological study of 49 cases. Tumori 2008; 94: 342-346.
22. Fararjeh A, Kaddumi E, Al-Khader A, Aburayyan W. The significance of StAR related lipid transfer protein-3 expression in breast cancer. Pol J Pathol 2022; 73: 215-222.
23. Vera-Sempere F, Llombart-Bosch A. Lipid-rich versus lipid-secreting carcinoma of the mammary gland. Pathol Res Pract 1985; 180: 553-558.
24. Zhang M, Pu D, Shi G, Li J. The clinical and pathological characteristics of lipid-rich carcinoma of the breast: an analysis of 98 published patients. BMC Womens Health 2023; 23: 301.
25. Russo S, Coppola D, Vinaccia P, et al. Lipid-rich histology in a basal-type immuno-profile breast carcinoma: a clinicopathological histochemical and immunohistochemical analysis of a case. Rare Tumors 2009; 1: e41.
26. Reis-Filho JS, Fulford LG, Lakhani SR, Schmitt FC. Pathologic quiz case: a 62-year-old woman with a 4.5-cm nodule in the right breast. Lipid-rich breast carcinoma. Arch Pathol Lab Med 2003; 127: e396-e398.
27. Gaspar BL, Kumar M, Gupta R, Garg R, Singh R, Vasishta RK. Lipid-rich Carcinoma of the breast with unusual clinical and histopathological features. Int J Surg Path 2016; 24: 538-542.

Address for correspondence

Prof. Nikola Živković
Department of Pathology
Faculty of Medicine Niš
University of Niš
Blvd. Dr Zorana Djindjića 81
18000 Niš, Serbia
e-mail: nikola.zivkovic@medfak.ni.ac.rs