CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Difficulties in histopathology diagnosis and treatment of depressive disorder of breast cancer in male – clinical case presentation

MARA JIDVEIAN POPESCU[1,2], AUREL SLABARU[3], ILEANA MARINESCU[4], ANDREI POPESCU[5], OVIDIU POPA-VELEA[1], ADELA MAGDALENA CIOBANU[6,7]

[1]*Department of Clinical Psychology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2]*Department of Oncology, No. 2 Railways Clinical Hospital, Bucharest, Romania*
[3]*Department of Surgery, No. 2 Railways Clinical Hospital, Bucharest, Romania*
[4]*Department of Psychiatry, University of Medicine and Pharmacy of Craiova, Romania*
[5]*Department of Oncology, "Colentina" Clinical Hospital, Bucharest, Romania*
[6]*Department of Psychiatry, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[7]*Department of Psychiatry, "Prof. Dr. Alexandru Obregia" Psychiatry Hospital, Bucharest, Romania*

Abstract

Breast cancer is less common among men than among women (about 1 in 100) and it is considered a rare disease but the evolution is significantly influenced by depression and distress. We present the case of a 63-year-old patient that was diagnosed in another Clinic with squamous skin carcinoma, but, after complete resection in our Hospital, it was proven to be breast cancer. At diagnosis, computed tomography (CT) scan showed local disease. Adjuvant treatment, consisting in chemotherapy and radiotherapy, was administered. At the beginning of hormonal therapy, the patient had a new CT scan that showed liver and bone metastases. The patient started palliative hormonal treatment with bisphosphonates. The aim of the study was to highlight both the importance of early diagnosis and treatment and the aggressiveness of male breast cancer compared with female. Depressive disorder and social distress worsens the prognosis and quality of life. Male with breast cancer has identity difficulties, body image disturbances and secondary distress.

Keywords: male, breast cancer, histopathology, diagnosis.

Introduction

Breast cancer is the second most frequent type of cancer, after lung, and the fifth cause of cancer related death, but only a small percent of the patients are male [1].

Because it is a very rare cancer in male population, screening is not recommended [2]. The association with breast cancer (*BRCA*) *1* and *2* genes is controversial, although the presence of these mutations is associated with higher risk of breast cancer in male (6% – 150–200 times higher than general population of men), about 81% of the cases have no family history of breast cancer. An association with gynecomastia and hormonal imbalance was shown [2–6].

Diagnosis methods are similar with those for female breast cancer and include: clinical examination, mammography, ultrasound of the breast and regional lymph nodes and biopsy. Additional computed tomography (CT) scan of the thorax and abdomen for determining tumor, node, metastasis (TNM) stage is needed [2].

Histopathology and immunostaining of male breast cancer is more similar to the post-menopausal female breast cancer [7, 8], but they have worse survival outcomes [9].

Treatment options are similar to those for female patients, surgery of the breast with lymph node dissection or sentinel lymph node biopsy (but no reconstruction is needed), radiation, chemotherapy and hormonal therapy. Regarding hormonal treatment, Tamoxifen is the preferred option [10–14].

The aim of the study was to highlight both the importance of early diagnosis and treatment and the aggressiveness of male breast cancer compared with female.

Case presentation

A 63-year-old man referred by the dermatologist to the Department of Surgery, with a mass on left breast. The tumor had been treated with topic lotions for several months, but it continued to grow in size.

The medical history revealed cardiac stent, hypertension and kidney stones, no signs of gynecomastia or hormonal imbalance. He had no family history of cancer.

Local examination identified a tumor in the upper-external quadrate of the left breast that was 5/4 cm, firm consistency, invading the skin. In the left axilla, there were two palpable lymph nodes (approximately 0.5 cm).

CT of the chest and abdomen was done and the result showed a tumor 5.6/4/3.5 cm in the left breast, with irregular contour, partially spiculiform, with heterogeneous structure and medium contrast that infiltrates the skin

and pectoral muscle. Axillary lymph nodes up to 1.3 cm, with low contrast and broken capsule (Figure 1, a and b).

Core biopsy was performed and histopathology result described two fragments of skin with neoplastic carcinomatous proliferation, with nodular-solid pattern, skin ulceration, pleading for squamous cell carcinoma of the skin, poor differentiation.

Immunostaining describes fragment with ulceration that has the aspect of epithelial tumor proliferation. The tumor cells are under the epidermis, invading the papillary and reticular derma, forming cellular cords and tumor mass made from atypically keratinocytes with agglomerated, pleomorphic and hyperemic nuclei, with numerous typical and atypical mitoses, with eosinophilic cytoplasm. No ductal differentiation is seen p63, cytokeratin (CK) 5/6, p40, CK34βE12, CK8/18 positive in tumor cells, gross cystic disease fluid protein-15 (GCDFP-15) focal positive, CK7, BerEP4, S100 protein (pS100), CK14, carcino-embryonic antigen (CEA), desmoglein-3 negative, Ki67 nuclear index approximately 80%. Conclusion: squamous cell carcinoma of the skin, poor differentiation, G3.

The patient presented with these results at the Department of Surgery, No. 2 Railways Clinical Hospital in Bucharest, Romania, where total mastectomy with lymph node dissection of the axilla was performed.

Histopathological analysis of the tumor mass

The macroscopic appearance of the surgically removed piece was a 12/10/5 cm mastectomy piece with tumor mass of 4.5 cm in the center, associated with ulceration of the skin. Macroscopic surgical limits without tumor infiltration. Microscopic evaluation of the tumor describes invasive ductal carcinoma, with poor differentiation. Lymph nodes from axilla (22), with tumor metastases and necroses, many tumor emboli in lymphatic vessels. Conclusion: invasive ductal carcinoma, pT4pN3Mx (Figures 2–7).

Immunostaining was performed and the result was a malignant tumor proliferation composed of large/medium cells, cohesive, with poorly visible cellular limits, abundant eosinophilic cytoplasm, arge nuclei, vacuolated, pleomorphic, some with distinct nucleoli and 9 mitoses/10 high-power fields (HPFs) (score 2). Tubule formation <10% (score 3), no carcinoma *in situ*. Extensive necrosis, no calcification, inflammation intra and near tumor. GATA-3 positive in tumor cells, p63 negative, estrogen receptor (ER) positive in 30% of tumor cells, Alred score = 6, progesterone receptor (PR) negative, Alred score = 0, Ki67 positive in 25% of tumor cells, human epidermal growth factor receptor 2 (HER2)/c-erbB2 = 0 (incomplete membrane staining on <30% of tumor cells). Conclusion: invasive breast cancer, Nottingham grade 2 (G2) (Figures 8–14).

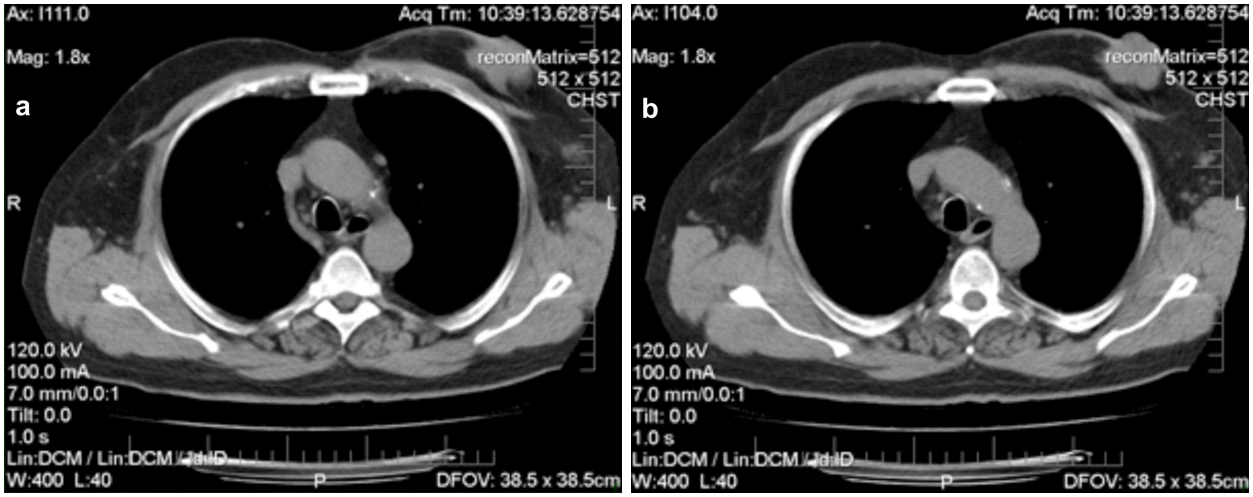

Figure 1 – ***(a and b) Computed tomography of thorax: large breast tumor that infiltrates the skin and pectoral muscle; in the axilla, there are enlarged lymph nodes.***

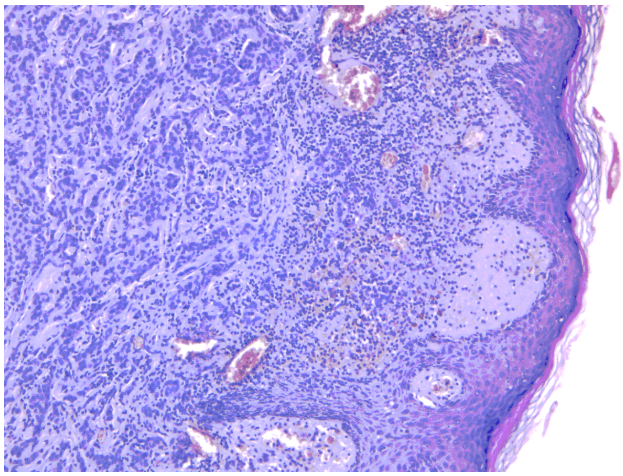

Figure 2 – ***Breast carcinoma invasive in dermis, without invading epidermis [Hematoxylin–Eosin (HE) staining, ×100].***

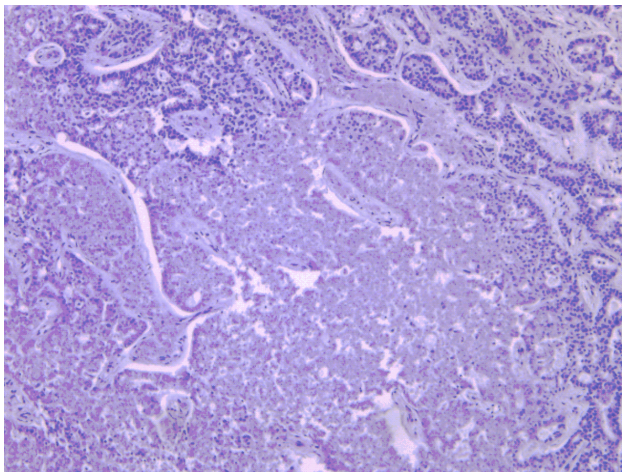

Figure 3 – ***Invasive breast carcinoma with skin ulceration and hemorrhage (HE staining, ×100).***

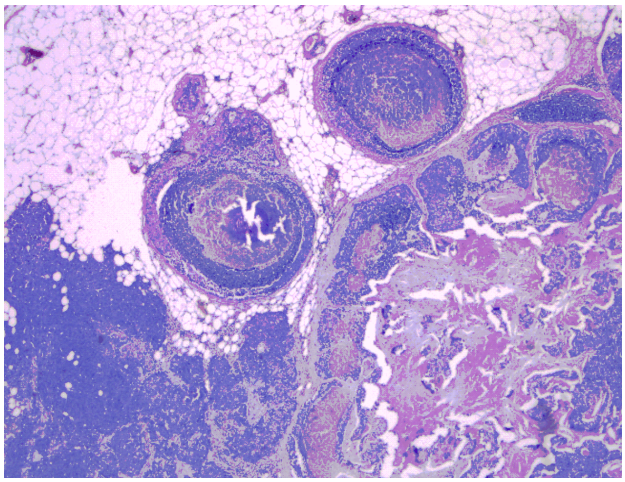

Figure 4 – ***Breast tumor biopsy with tumor necrosis (HE staining, ×100).***

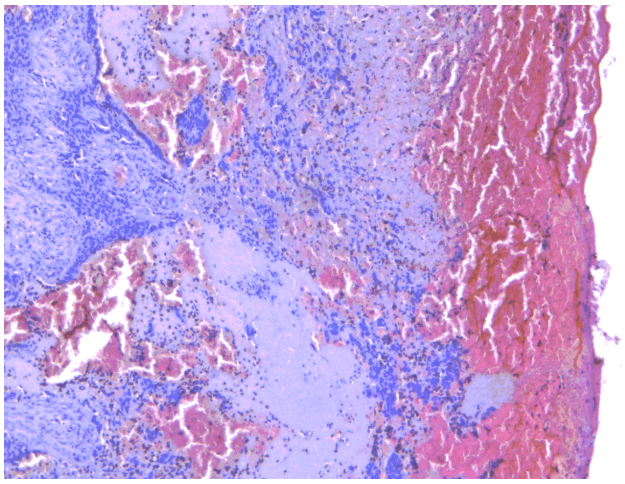

Figure 5 – ***Breast tumor with lympho-vascular indirect invasion (orphaned artery) (HE staining, ×100).***

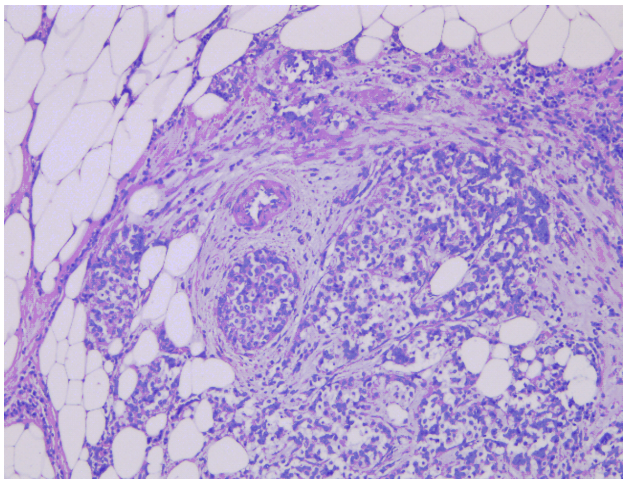

Figure 6 – ***Tumor lymph node, with carcinomatous cells in adjacent vessels (HE staining, ×25).***

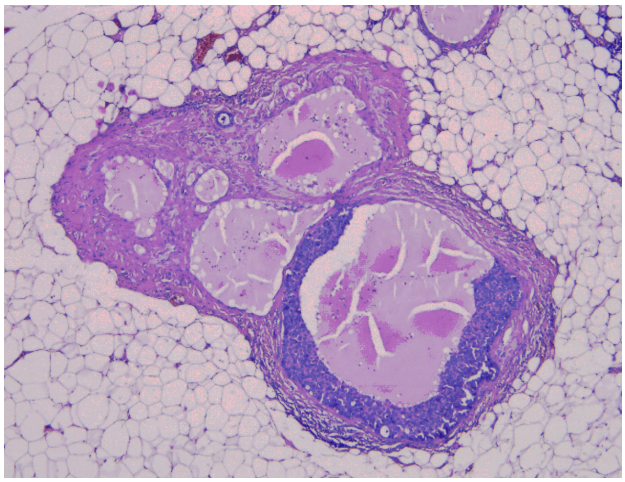

Figure 7 – ***Breast tumor with tumor intravascular emboli (HE staining, ×50).***

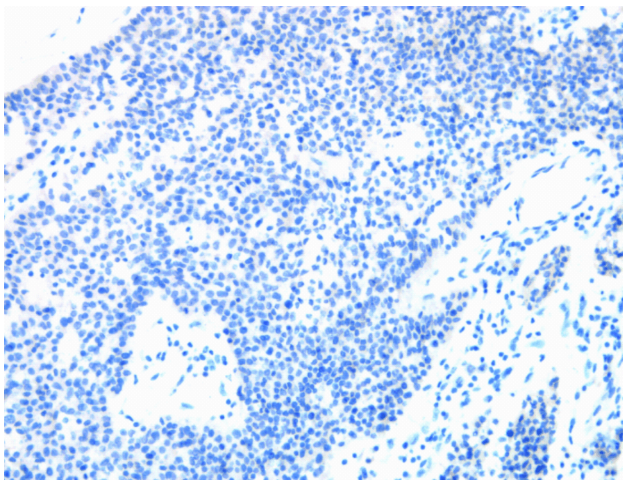

Figure 8 – ***Invasive breast carcinoma with negative androgen receptor (AR) (Anti-AR antibody immuno-marking, ×200).***

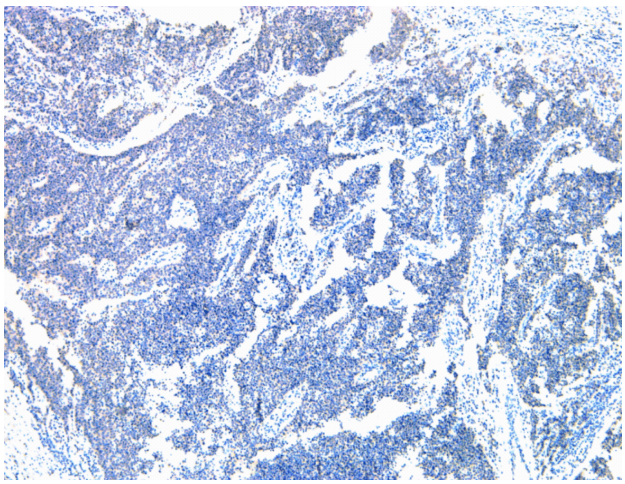

Figure 9 – ***Invasive breast carcinoma with negative progesterone receptor (PR) (Anti-PR antibody immuno-marking, ×50).***

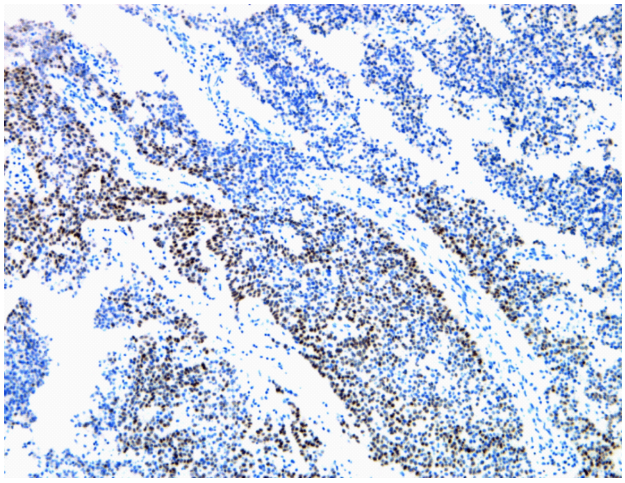

Figure 10 – ***Invasive breast carcinoma with positive estrogen receptor (ER) of 60% in tumor cells (Anti-ER antibody immunomarking, ×100).***

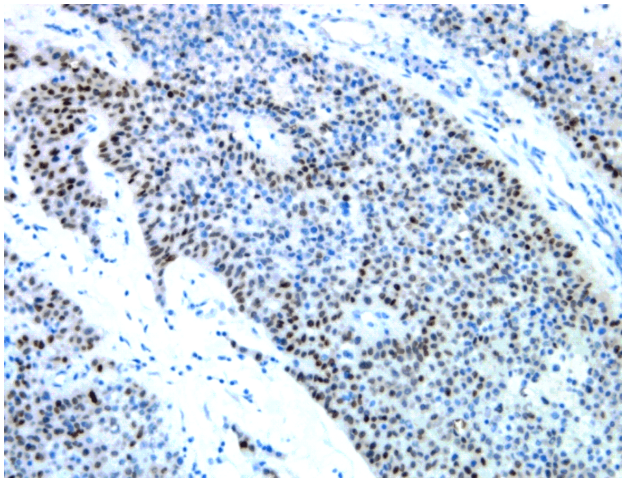

Figure 11 – ***Invasive breast carcinoma with positive estrogen receptor (ER) of 60% in tumor cells (Anti-ER antibody immunomarking, ×200).***

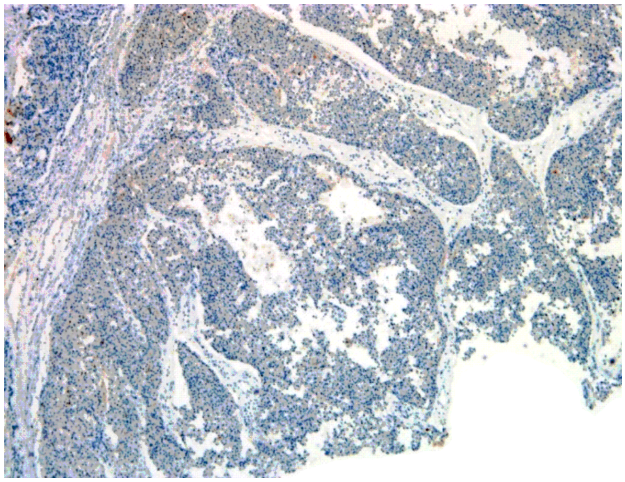

Figure 12 – ***Invasive breast carcinoma with negative expression of HER2/c-erbB2, score = 0 (incomplete membrane staining on <30% of tumor cells) (Anti-HER2/c-erbB2 antibody immunomarking, ×50). HER2: Human epidermal growth factor receptor 2.***

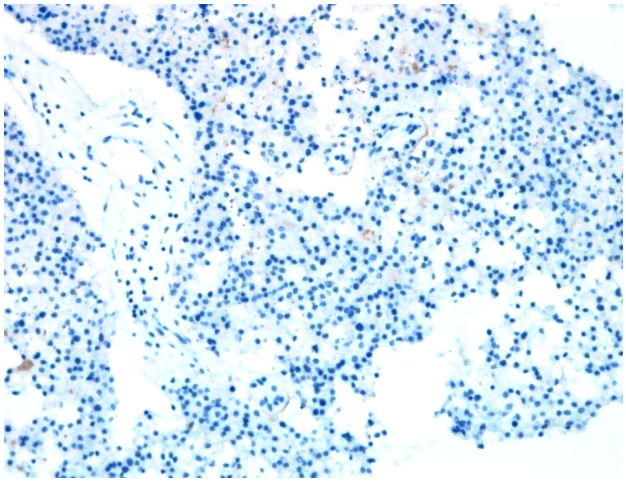

Figure 13 – ***Invasive breast carcinoma with negative expression of Her2/c-erbB2, score = 0 (incomplete membrane staining on <30% of tumor cells) (Anti-HER2/c-erbB2 antibody immunomarking, ×200). HER2: Human epidermal growth factor receptor 2.***

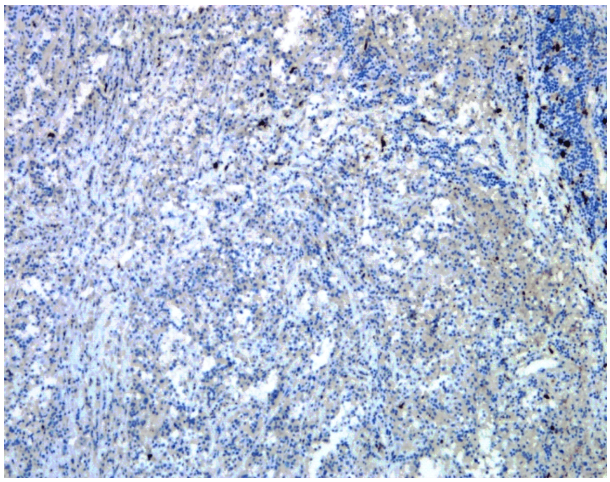

Figure 14 – ***Invasive breast carcinoma with low Ki67 expression in tumor cells (<5%) (Anti-Ki67 antibody immunomarking, ×100).***

Treatment

After surgery, the patient started adjuvant chemotherapy (4 Anthracycline + Cyclophosphamide – 4 Docetaxel), local radiotherapy on chest wall and axilla, followed by hormonal therapy. At the beginning of hormonal therapy, a CT of the thorax and abdomen was performed and the result showed no signs of local relapse, but there were mediastinal lymph nodes of 2.1/1.2 cm, and multiple bone lesions (Figures 15 and 16).

At this time, the patient started deploying a depressive symptomatology dominated by anhedonia, sleep disturbances, suicidal ideation and anxiety. We decided to perform a psychiatric evaluation. He was given Depression, Anxiety and Stress Scale – 21 Items Revised (DASS-21R) questionnaire for depression, anxiety and stress, Rosenberg Self-Esteem Scale and Cognitive Emotion Regulation Questionnaire (CERQ) for emotional–cognitive coping style. The results showed a high level of self-esteem, moderate

level of depression, but severe level of anxiety and stress. The predominant emotional coping styles used were positive refocus, refocus on planning, positive reevaluation and perspective. He was started on anxiolytic therapy.

The patient continued with hormonal therapy in the metastatic setting (Tamoxifen), with good tolerance to treatment and came for regular scanning. He responded to the hormonal treatment for two years (regression of lymph nodes and stable disease on the bone metastases). During this time, his mental status improved. We did a new psychological evaluation after 18 months and the results were similar for coping styles and self-esteem scale, but he had a low level of depression, stress and anxiety (within normal spectrum).

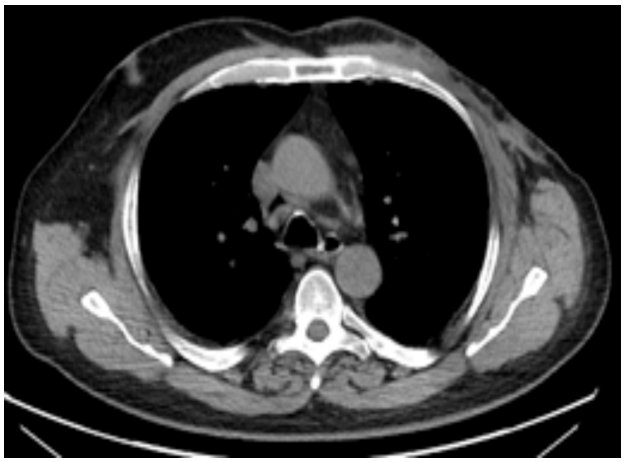

Figure 15 – ***Computed tomography of thorax that shows bone metastases at the vertebral level.***

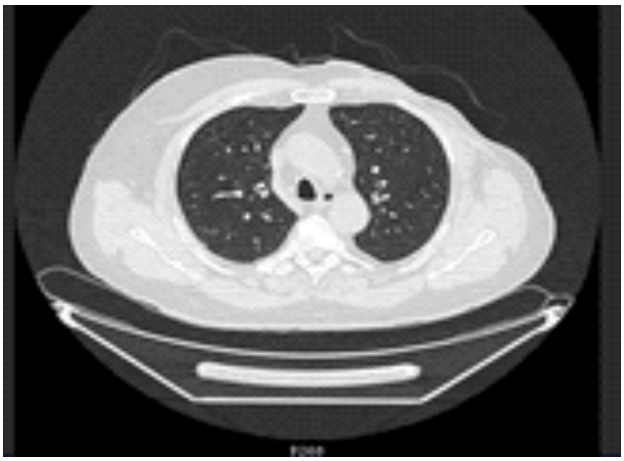

Figure 16 – ***Computed tomography of thorax that shows no local or axillar recurrence.***

Discussions

We presented a rare case of male breast cancer with, apparently, no risk factors (family history, gynecomastia, hormonal imbalance, diabetes, obesity, Klinefelter syndrome, cholelithiasis [15] that was diagnosed in an advanced stage and did not respond to intensive course of chemotherapy.

Male breast cancer is very rare (less than 1% of all male cancers and is responsible for less than 0.1% of all male cancer related deaths [16], but there has been a rise in the incidence from 1/100 000 cases to 1.2/100 000 between 1970 and 2004 [17, 18]. The average age of diagnosis is 60 to 70 years old (about 10 years later than women [19], but it can appear in younger men and children [16].

At presentation, most patients present with palpable mass in the breast (about 75%), but can also have nipple retraction, serous discharge, or ulceration. Usually, male breast cancer patients have a higher stage of disease at diagnosis compared to women, which happens because there is a medium time lapse between symptoms and consultation of six to 12 months [16].

Histopathological characteristics of male breast cancer are similar to women breast cancer; the most common pattern (85%) is poorly differentiated infiltrating ductal carcinoma. Immunostaining is represented by a strongly positive hormonal receptor tumors [ER 85–90%, PR 90–95%, androgen receptor (AR) 90–95% – associated with good prognosis], but HER2 is positive more common in younger patients (less than 45 years old) and it is associated with poor prognosis [16, 20].

Treatment options are similar to female breast cancer, but, usually, these patients have worse outcome because of late diagnosis [19]. Poor prognostic factors include, as in women, large tumors, lymphatic tumor emboli, poor histological differentiation, HER2 positivity, p53 expression and the amplification of cyclin D1 (CCND1) (11q13) [16].

Our patient had multiple poor prognostic factors, as he presented with a large and infiltrating tumor that was described as pT4, invasion in axilla lymph nodes (pN3), many tumor embolus in lymphatic vessels, poorly differentiated invasive ductal carcinoma, with no PR expression, low ER expression (30%) and Ki67 >20%.

Despite intensive adjuvant chemo- and radiotherapy, the patient presented multiple metastases at six months after surgery. Palliative hormonal therapy with Tamoxifen was considered the best option according to both *European Society for Medical Oncology* (ESMO) and *National Comprehensive Cancer Network* (NCCN) Guidelines [21, 22]. The patient had partial response on the metastatic lymph nodes and stable disease on bone for more than two years, with no significant side effects.

About 50% of breast cancer patients present symptoms of depression [23], and 10–25% of them have severe depression disorder [24]. Anxiety disorder is also frequent in breast cancer patients, about 24% of them being diagnose [25]. The treatment for depression and anxiety associated with breast cancer is difficult and needs to be personalized. Depressive and anxious symptoms appear and evolve gradually. An important traumatic factor is the moment of diagnosis, which is accompanied by increased stress and implicitly activation of the hypothalamic–pituitary–adrenal (HPA) axis. Activation of the HPA axis causes an endogenous cytokines that amplifies pro-inflammatory factors, endothelial dysfunction decreasing immunity and thus favoring tumor progression and metastatic invasion. In the case of male breast cancer, stress and depression are amplified by stigma and by the refusal of the patient to suffer from an illness that is specific for women [26].

Stigma, depression, fear and the idea that men could not have breast cancer, are involved in late diagnosis of the

patients. Depression increases with surgical intervention (postoperative depression), which psychologically amplifies distress, refusing the female condition of the disease, and intensely experiencing body image mutilation [27]. Using estrogen inhibitors, hormone therapy can amplify depression and favor suicidal ideation. Depression therapy requires avoidance of cytochrome P450 2D6 (CYP2D6) antidepressant drugs, which significantly reduces the efficacy of Tamoxifen estrogen-inhibiting medication, favoring recurrences and metastatic invasion [28], as well as therapeutic resistance to antidepressant medication [29], resistance enhanced by the association of estrogen inhibitors in breast cancer men [30]. The prophylactic therapeutic use of Venlafaxine/Desvenlafaxine and Tamoxifen therapy or anticonvulsant molecules that interfere minimally with CYP2D6 is considered as a proper therapeutic attitude. The use of other serotonin augmentative antidepressants may augment hyponatremia, a condition also favored by the carcinoma and oncology therapies [31] and prolactinemia and gynecomastia condition stigmatizing for men with breast cancer [32]. Severe hyponatremia leads to deterioration of cognitive and somatic state with increased cardio- and cerebrovascular risk (Figure 17).

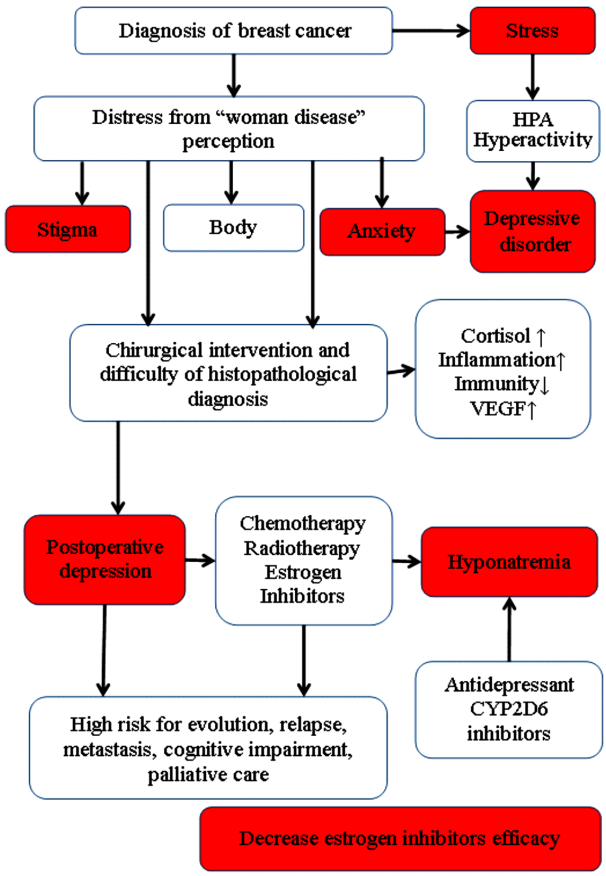

Figure 17 – ***Difficulties and clinical particularities of the diagnosis and therapeutic effects of depressive disorder in male breast cancer. CYP2D6: Cytochrome P450 2D6; HPA: Hypothalamic–pituitary–adrenal (axis); VEGF: Vascular endothelial growth factor.***

Conclusions

Male breast cancer has to be taken into consideration when gynecomastia or a tumor mass is observed and proper investigations have to be done from the beginning, including mammography and/or ultrasound of breast and axilla, CT of thorax and abdomen, core biopsy with histopathological and immunohistochemical (ER, PR, AR and HER2 immunomarkers) analyses. Dysmorphic distress delays a lot medical evaluation and the disease is diagnosed in advanced stages, associated frequently with depression, anxiety and body dysmorphic disorder. More investigations are needed for risk factors associated with male breast cancer and the possibility to define a risk group for whom screening is needed.

Depressive disorder is a risk factor for poor prognosis of male breast cancer and other forms of cancer that stigmatize male image of man. It requires early diagnosis and a personalized therapeutic attitude, in which the use of antidepressant medication would be the correct option. This attitude can improve cancer evolution and quality of life. Depressive disorder and distress condition may be real risk factors for breast cancer in men.

Conflict of interests

No conflict of interests to declare.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018, 68(6):394–424.

[2] Sencha AN (ed). Imaging of male breast cancer. Springer International Publishing, Switzerland, 2015.

[3] Basham VM, Lipscombe JM, Ward JM, Gayther SA, Ponder BAJ, Easton DF, Pharoah PDP. *BRCA1* and *BRCA2* mutations in a population-based study of male breast cancer. Breast Cancer Res, 2002, 4(1): R2.

[4] Ottini L, Masala G, D'Amico C, Mancini B, Saieva C, Aceto G, Gestri D, Vezzosi V, Falchetti M, De Marco M, Paglierani M, Cama A, Bianchi S, Mariani-Costantini R, Palli D. *BRCA1* and *BRCA2* mutation status and tumor characteristics in male breast cancer: a population-based study in Italy. Cancer Res, 2003, 63(2):342–347.

[5] Ottini L, Silvestri V, Rizzolo P, Falchetti M, Zanna I, Saieva C, Masala G, Bianchi S, Manoukian S, Barile M, Peterlongo P, Varesco L, Tommasi S, Russo A, Giannini G, Cortesi L, Viel A, Montagna M, Radice P, Palli D. Clinical and pathologic characteristics of *BRCA*-positive and *BRCA*-negative male breast cancer patients: results from a collaborative multicenter study in Italy. Breast Cancer Res Treat, 2012, 134(1):411–418.

[6] Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for *BRCA1* mutation carriers identified in a risk evaluation program. J Natl Cancer Inst, 2002, 94(18):1365–1372.

[7] Anderson WF, Althuis MD, Brinton LA, Devesa SS. Is male breast cancer similar or different than female breast cancer? Breast Cancer Res Treat, 2004, 83(1):77–86.

[8] Hill TD, Khamis HJ, Tyczynski JE, Berkel HJ. Comparison of male and female breast cancer incidence trends, tumor characteristics, and survival. Ann Epidemiol, 2005, 15(10): 773–780.

[9] Liu N, Johnson KJ, Ma CX. Male breast cancer: an updated surveillance, epidemiology, and end results data analysis. Clin Breast Cancer, 2018, 18(5):e997–e1002.

[10] Veronesi U, Goldhirsch A, Veronesi P, Gentilini OD, Leonardi MC (eds). Breast cancer: innovations in research and management. Springer International Publishing, 2017.

[11] Golshan M, Rusby J, Dominguez F, Smith BL. Breast conservation for male breast carcinoma. Breast, 2007, 16(6): 653–656.

[12] Albo D, Ames FC, Hunt KK, Ross MI, Singletary SE, Kuerer HM. Evaluation of lymph node status in male breast cancer patients: a role for sentinel lymph node biopsy. Breast Cancer Res Treat, 2003, 77(1):9–14.

[13] Gentilini O, Chagas E, Zurrida S, Intra M, De Cicco C, Gatti G, Silva L, Renne G, Cassano E, Veronesi U. Sentinel lymph node biopsy in male patients with early breast cancer. Oncologist, 2007, 12(5):512–515.
[14] France L, Michie S, Barrett-Lee P, Brain K, Harper P, Gray J. Male cancer: a qualitative study of male breast cancer. Breast, 2000, 9(6):343–348.
[15] Onami S, Ozaki M, Mortimer JE, Pal SK. Male breast cancer: an update in diagnosis, treatment and molecular profiling. Maturitas, 2010, 65(4):308–314.
[16] Diez Freire CC. Male breast carcinoma – general. Pathology Outlines.com, http://www.pathologyoutlines.com/topic/breastmalignantmalecarcinoma.html, January 2019.
[17] Cutuli B, Le-Nir CC, Serin D, Kirova Y, Gaci Z, Lemanski C, De Lafontan B, Zoubir M, Maingon P, Mignotte H, de Lara CT, Edeline J, Penault-Llorca F, Romestaing P, Delva C, Comet B, Belkacemi Y. Male breast cancer. Evolution of treatment and prognostic factors. Analysis of 489 cases. Crit Rev Oncol Hematol, 2010, 73(3):246–254.
[18] Speirs V, Shaaban AM. The rising incidence of male breast cancer. Breast Cancer Res Treat, 2009, 115(2):429–430.
[19] Sanguinetti A, Polistena A, Lucchini R, Monacelli M, Galasse S, Avenia S, Triola R, Bugiantella W, Cirocchi R, Rondelli F, Avenia N. Male breast cancer, clinical presentation, diagnosis and treatment: twenty years of experience in our Breast Unit. Int J Surg Case Rep, 2016, 20(Suppl):8–11.
[20] Voinea OC, Cîrstoiu MM, Ion D, Sajin M, Dumitru AD, Patrascu OM, Jinga DC, Nica AE. Histology of male breast lesions. Series of cases and literature review. Maedica (Bucharest), 2018, 13(3):196–201.
[21] National Comprehensive Cancer Network (NCCN). Breast cancer. NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines®, version 1.2019, March 14, 2019.
[22] Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E; on behalf of the ESMO Guidelines Committee. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2019, 30(8):1194–1220.
[23] Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr, 2004, 2004(32):57–71.
[24] Tsaras K, Papathanasiou IV, Mitsi D, Veneti A, Kelesi M, Zyga S, Fradelos EC. Assessment of depression and anxiety in breast cancer patients: prevalence and associated factors. Asian Pac J Cancer Prev, 2018, 19(6):1661–1669.
[25] Kadan-Lottick NS, Vanderwerker LC, Block SD, Zhang B, Prigerson HG. Psychiatric disorders and mental health service use in patients with advanced cancer: a report from the coping with cancer study. Cancer, 2005, 104(12):2872–2881.
[26] Midding E, Halbach SM, Kowalski C, Weber R, Würstlein R, Ernstmann N. Men with a "woman's disease": stigmatization of male breast cancer patients – a mixed methods analysis. Am J Mens Health, 2018, 12(6):2194–2207.
[27] Brain K, Williams B, Iredale R, France L, Gray J. Psychological distress in men with breast cancer. J Clin Oncol, 2006, 24(1): 95–101.
[28] Aguiar CCT, Aguiar JVA, Rocha MG. Treatment of depression in patients under breast cancer therapy: antidepressant–tamoxifen drug interactions. J Drug Metab Toxicol, 2017, 8(2):228.
[29] Marinescu I, Vasiliu O, Vasile D. Translational approaches in treatment-resistant depression based on animal model. Rom J Morphol Embryol, 2018, 59(3):955–964.
[30] Wibowo E, Pollock PA, Hollis N, Wassersug RJ. Tamoxifen in men: a review of adverse events. Andrology, 2016, 4(5): 776–788.
[31] Bowman BT. Electrolyte disorders associated with cancer. J Onco-Nephrol, 2017, 1(1):30–35.
[32] Ciobanu AM, Popa C, Marcu M, Ciobanu CF. Psychotic depression due to giant condyloma Buschke–Löwenstein tumors. Rom J Morphol Embryol, 2014, 55(1):189–195.

Corresponding author
Ileana Marinescu, Lecturer, MD, PhD, Department of Psychiatry, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40351–443 522, e-mail: marinescu_psy@yahoo.com

Received: March 3, 2019

Accepted: November 8, 2019