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Breast invasive lobular carcinoma: a retrospective clinicopathologic study of 25 cases

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Abstract

Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer, having distinct prognostic and biologic implications. As an objective of the present work, we analyzed the clinicopathologic characteristics and prognostic factor of this invasive breast cancer variant. Clinical and morphological data of 25 cases of ILC collected during 2006–2011 were reviewed. Histopathologically, 11 cases were of classic type, and the others were non-classic with solid and histiocytoid subtypes being mostly encountered. Overall the non-classic ILC type was diagnosed in more aged patients (with a median age at onset of 59 years), with a predominance for a more advanced tumor degree differentiation (78.5% as grade 2 and 3), in advanced pTNM stages (50% in stage III and IV), with 50% lymph node involvement and with over 70% ER and Her2 reactivity. Statistically, we found that for the solid variant prevailed a PR+ and Her2- status while in histiocytoid subtype the PR- and Her2+ immunoprofile was most encountered. We conclude that non-classic ILC type represents a distinct entity of invasive breast carcinoma with a worsen prognostic than the conventional ILC type.

***Keywords*:** breast cancer, invasive lobular carcinoma, classic variant, clinicopathological, receptors status.

Introduction

Invasive lobular carcinoma (ILC) is the second most common overall type of breast cancer, accounting for 5–15% of the cases in most Western reports [1–4]. Data from the literature reported an increasing incidence of ILC, respectively between 1987 and 1999 it increased 1.52-folds [3, 5]. This trend was observed especially amongst postmenopausal women [3] and seems to be related to the use of hormonal therapy [2, 6, 7].

Its early diagnosis is very difficult because of the specific targetoid growth of lobular tumor cells [1]. The morphological diagnosis is also challenging due to several distinct variants of ILC that have been reported [8–13]. Therefore, this type of breast cancer seems to have a distinctive clinicopathologic profile, being quite often multifocal and multicentric [1, 14], having a higher risk of bilateralism [15], large tumor sizes, lower histologic grade [16], a higher rate of multiple metastases [17], a distinct pattern of involvement of distant sites [18–20], a trend towards later locoregional recurrence [21, 22], and a lower rate of lymphatic-vascular invasion [23]. Also, its immunophenotype is distinctive, ILC frequently expressing hormone receptors and bcl-2, but losing the E-cadherin expression, c-erbB-2 and p53 [1, 2, 16, 24–29]. In terms of prognosis, the literature data is still controversial, with most studies documenting a prognosis comparable to that of the stage-matched and grade-matched invasive ductal carcinomas [1, 14, 19, 30]. In addition, it seems that ILC is less responsive to chemotherapy [21, 31, 32], is not suited for Herceptin® (trastuzumab) treatment [1, 24, 33], while these patients can benefit from the hormonal therapy [6, 32].

The objective of this study was to report our experience in diagnosis of breast adenocarcinoma and to evaluate the major clinicopathological factors that might be involved in the prognosis of these patients.

Materials and Methods

We reviewed here the medical records from the Pathology Laboratory of the Emergency County Hospital of Craiova and identified those patients who had been operated for breast carcinomas from 2006 through 2011. Two-experienced pathologist independently reviewed the original histopathologic material to certify the breast ILC diagnosis according to the *WHO* criteria (2003) [34]. As clinical-morphological data, we kept each patient's age, the histopathological variant, histological differentiation degree, pTNM, N stage, and the combined ER, PR, and HER2/neu status (Table 1). The casuistry was histopathologically subclassified into one of the following *WHO* breast ILC subtypes: classic, alveolar, solid, tubulolobular, trabecular and other

(pleomorphic, signet ring, histiocytoid, and apocrine). The histological differentiation degree was assessed according to the criteria of Elston CW and Ellis IO [35], based on the combined assessment of tubule formation, nuclear grade, and mitotic activity, into well (grade 1), moderately (grade 2) or poorly (grade 3) differentiated forms. Tumor stages were determined based on the criteria described in the 6th edition of the *American Joint Committee on Cancer* (AJCC) staging manual [36].

The combined receptor status was assessed as six-level categorical profiles: ER-, PR-, Her2-; ER-, PR-, Her2+; ER+, PR-, Her2-; ER+, PR-, Her2+; ER+, PR+, Her2- and ER+, ER+, PR+, Her2-.

Table 1 – ***The major clinico-pathological features of the investigated breast adenocarcinoma cases***

ILC subtypes (No. of cases)	Age [years]	Grade			pTNM				N		ER-, PR-, Her2 status					
		1	*2*	*3*	*I*	*II*	*III*	*IV*	*N0*	*N+*	*ER- PR- Her2-*	*ER- PR- Her2+*	*ER+ PR- Her2-*	*ER+ PR- Her2+*	*ER+ PR+ Her2-*	*ER+ PR+ Her2+*
Classic (1)	45	+			+				+					+		
Classic (2)	56	+				+			+					+		
Classic (3)	58		+			+				+					+	
Classic (4)	62		+				+			+					+	
Classic (5)	64		+			+			+				+			
Classic (6)	55	+			+				+				+			
Classic (7)	61		+			+				+					+	
Classic (8)	53				+				+					+		
Classic (9)	57	+			+				+		+					
Classic (10)	58	+				+				+					+	
Classic (11)	69		+			+			+					+		
Alveolar (1)	57	+				+			+						+	
Solid (1)	59		+			+			+						+	
Solid (2)	62		+				+			+						+
Solid (3)	65			+			+			+					+	
Solid (4)	67			+				+		+					+	
Tubulolobular (1)	49	+			+				+					+		
Tubulolobular (2)	55	+				+			+					+		
Trabecular (1)	51		+				+			+				+		
Pleomorphic (1)	58		+			+			+			+				
Pleomorphic (2)	63			+			+			+						+
Histiocytoid (1)	58		+			+			+					+		
Histiocytoid (2)	61		+				+			+		+				
Histiocytoid (3)	62		+				+			+		+				
Histiocytoid (4)	59	+				+			+							+

Histopathological processing

Paraffin blocks from the reviewed breast ILC cases were process by classical histological techniques (HE stain) and for a more detailed histopathological investigation were stained with Masson's trichrome kit (BioOptica, Albedo, Romania, code 21-010802IC) and Alcian Blue pH 2.5–PAS stain (BioOptica, Albedo, Romania, code W01030799).

Immunohistochemical processing

As amplification method we used the Streptavidin–Biotin peroxidase technique performed with LSAB2 (Dako, Redox, Romania, code K0675) and the following primary antibodies: ER (1D5, mouse anti-human, monoclonal, Dako, Redox, Romania, code M7047) diluted as 1:40, PR (PgR 636, mouse anti-human, monoclonal, Dako, Redox, Romania, code M3569) diluted as 1:40, and c-erbB-2 (polyclonal rabbit anti-human, Dako, Redox, Romania, code A0485) diluted as 1:300. The sections were first processed by 20 minutes heat induced epitope retrieval in DakoCytomation Target Retrieval solution, code S1700, and then the endogenous peroxidase activity was blocked with 3% hydrogen peroxide in PBS for 15 minutes and the unspecific binding sites were blocked with 5% BSA/PBS for one hour. The primary antibodies were incubated overnight at 4^0C and then to visualize the signal, we followed the standard LSAB2 protocol. As chromogen we used 3,3'-diaminobenzidine tetrahydrochloride (Dako, Redox, Romania, code K3468) and for nuclei counterstaining Mayer's Hematoxylin. Negative controls were obtained by omitting the primary antibodies, and as external positive control were used normal breast tissues specimens.

Immunostaining assessment was performed independently by two-experienced pathologist and, in case of disagreement; the cases were reviewed until a consensus was reached. The ER and PR were scored semi-quantitatively, on ×400 magnification by evaluating the percentage and intensity of stained tumor nuclei using the H-score [37]. A negative reaction was defined as a score of ≤ 00, and positive as > 200. For c-erbB-2 we used the original HercepTest (DAKO) scoring criteria, using a 0–3+ scale. The examination was performed on ×200 magnification and scores of 0 and 1+ were considered negative, while scores of 2+ and 3+ were assessed as positive.

The images were acquired using a Nikon Eclipse 55i microscope (Nikon, Apidrag, Bucharest) equipped with a 5-megapixel cooled CCD camera and the Image ProPlus AMS7 software (Media Cybernetics Inc., Buckinghamshire, UK).

Statistical analysis was performed with SPSS version 11.0 for Windows. Given the small number of some of the ILC histopathological variants, to achieve significance for different tests, we have grouped investigated cases in two broad categories: classic ILC and non-classic ILC (which included the other ILC subtypes). To test for different age influence on different parameters, we divided the data as below and above the median age values. To assess the categorical variables and the association between ER, PR and c-erbB-2 expression and other clinicopathologic variables we used the chi square test, the results being considered statistically significant if the *p*-value was <0.05. For multiple groups comparisons ANOVA testing was used.

Results

According to the data presented in Table 1, the general median onset age was of 58 years (range: 45–69 years) with a slight tendency for the non-classic cases to develop in older people. In most cases, the tumor degree was 2 (48%) but in the classic subtype grade 1 prevailed (63.63%). Regarding the stage of the disease and lymph node status, we observed that while most of the cases were in the stage II (48%) and with no lymphatic metastases (60%), the non-classical variants have been diagnosed more frequently in more advanced stages (50% of these in stage III) and with lymph node metastasis (in 42.85% of these cases).

Histopathologically, our casuistry of breast ILC during the last six years was dominated by the classical type with 11 cases (44%), followed by the solid subtype with four cases (16%) and histiocytoid variant with four cases. The tubulolobular and plemorphic subtypes were diagnosed in two cases each one, while the alveolar and trabecular subtypes have been found only in a single case each.

Typically, for the classic type, the tumor cells are discohesive, loosely dispersed throughout a fibrous matrix, either encircling ducts and lobules (targetoid pattern), either growing in single file (Indian file pattern) (Figure 1, A and B). Generally, the stroma had a fibrous aspect with variable density and in some areas we observed a dense lymphoid infiltrate. At the cellular level, we have distinguished two subtypes: those that were uniform, with scant cytoplasm and bland nuclei with inconspicuous nucleoli, roughly 1.5 times the size of a lymphocyte (type A) and those with more abundant cytoplasm and larger nuclei with more conspicuous nucleoli (type B). In six cases, in the nearby vicinity, we noticed the presence of lobular carcinoma *in situ*. In four of these cases, the histopathological aspect was of a typical lobular carcinoma *in situ* with a monotonous, discohesive proliferation of round, slightly hyperchromatic cells that were evenly spaced, distending and filling acinar lumina (Figure 1C). In the remaining cases, we observed a pleomorphic lobular carcinoma *in situ*, which exhibited discohesive larger cells with abundant cytoplasm and a greater degree of nuclear pleomorphism, and more obvious nucleoli. Other observed histologic findings were: small areas of other histological subtypes (pleomorphic – two cases, histiocytoid – two cases, tubulolobular – one case, solid – one case), infiltrative growth in to the surrounding breast tissues, perineural invasion (three cases), lymphatic vascular invasion (four cases) and blood vascular invasion (three cases). Regarding the differentiation degree we noticed the prevalence of grade 1 (seven cases), the remaining cases being classified as grade 2 (four cases). Most of these cases were pTNM staged as II (six cases) and I (four cases) and lymph node metastasis was noticed only in four cases. Concerning hormonal receptors and Her2 status, we observed that most of the cases were ER+ (10 cases), almost half of them were PR+, and only for cases presented Her2 reactivity (Figure 1, D and F). The analysis of the combined receptor status showed that the most encountered immunoprofiles were ER+PR+Her2- (four cases) and ER+PR-Her2+ (three cases) profiles.

Descriptive statistical data of the cases identified as classical type were grouped considering the median age of this group (58-year-old). The percentage of ER+ *vs.* ER- hormonal status did not differ for the groups with ages <58 years and >58 years, $\chi^2(1, N=11)=1.320$, $p=0.251$. There was no difference in the distribution of ER status between the tumor grades 1 and 2, $\chi^2(1, N=11)=0.629$, $p=0.428$. There was no difference in the distribution of ER status over the pTNM stages I, II and III, $\chi^2(2, N=11)=1.925$, $p=0.382$. There was no difference in the distribution of ER status over the lymph node invasion status, $\chi^2(1, N=11)=0.629$, $p=0.428$. The distribution of PR- hormonal status was more frequent among patients with ages <58 years, while the PR+ hormonal status was more frequent among patients with ages >58 years, $\chi^2(1, N=11)=7.639$, $p=0.006$. There was no difference in the distribution of PR status between the tumor grades 1 and 2 $\chi^2(1, N=11)=2.213$, $p=0.137$. There was no difference in the distribution of PR status over the pTNM stages I, II and III, $\chi^2(2, N=11)=5.622$, $p=0.060$.

Most PR+ tumors were related to invaded lymph node (N1), $\chi^2(1, N=11)=7.513$, $p=0.006$. The percentage of Her2+ *vs.* Her2- status did not differ for the groups with ages <58 years and >58 years, $\chi^2(1, N=11)=2.213$, $p=0.137$. There was no difference in the distribution of Her2 status between the tumor grades 1 and 2, $\chi^2(1, N=11)=3.592$, $p=0.058$. There was no difference in the distribution of Her2 status over the pTNM stages I, II and III, $\chi^2(2, N=11)=0.917$, $p=0.632$. There was no difference in the distribution of HER2 status over the lymph node invasion status, $\chi^2(1, N=11)=0.3592$, $p=0.058$.

Solid type was diagnosed in four cases with the patients' age being greater than the general median age at onset. Microscopically these tumors were composed of large solid sheets with little intervening stroma, which diffusely infiltrated the surrounding tissues (Figure 2, A and B). Tumor cells had the same cytological features as those from classic lobular carcinoma. In two

cases the degree of differentiation was 2 and in the other cases was 3, and all four cases presented perineural invasion (Figure 2C), blood and lymphatic vascular invasion.

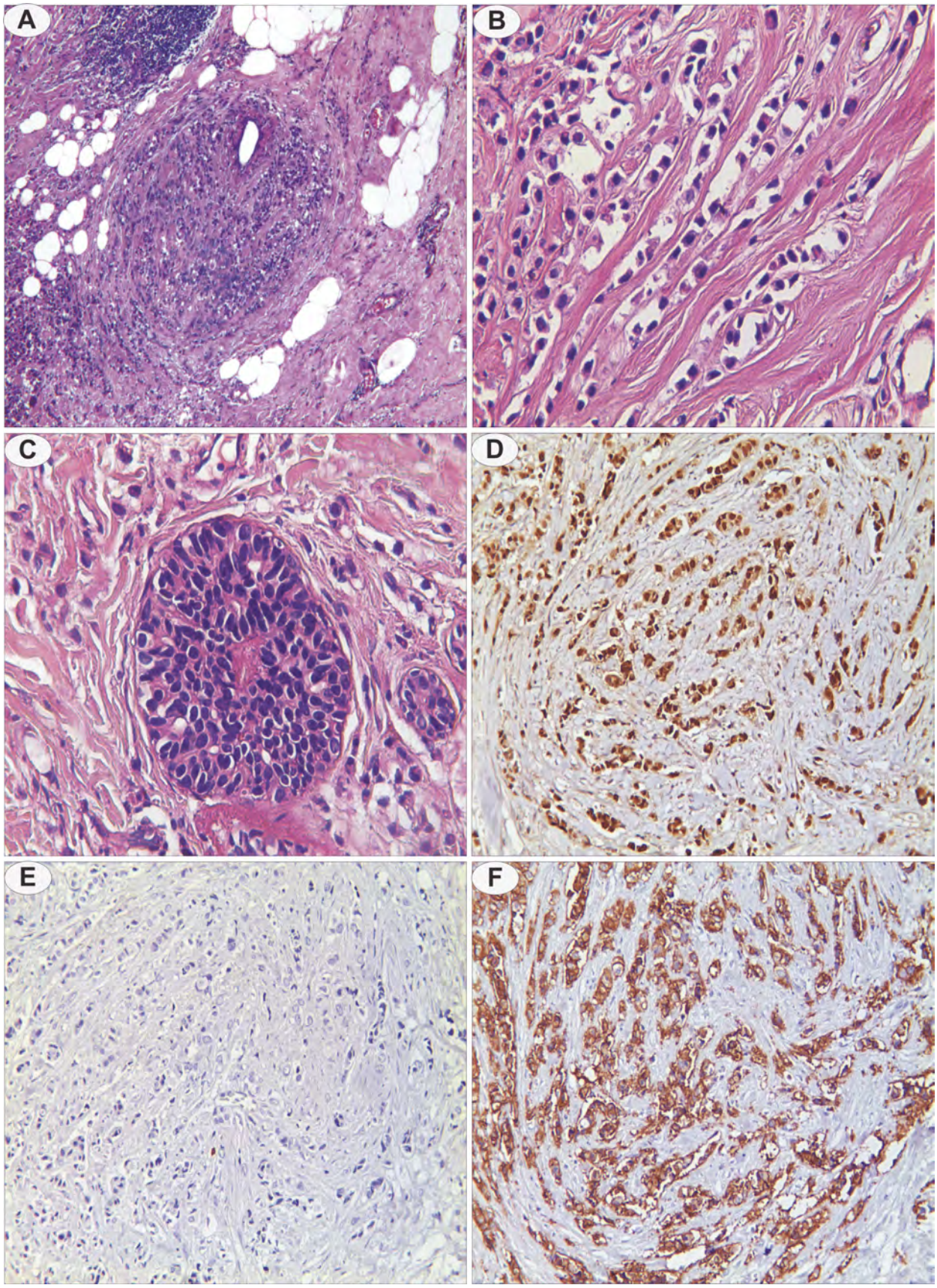

Figure 1 – ***Breast invasive lobular carcinoma – classical type: (A and B) Targetoid and Indian file growth patterns (HE stain, ×40/×200); (C) Typical lobular carcinoma "in situ" (HE stain, ×200); (D) ER+ in the nucleus of neoplastic cells (DAB, ×100); (E) PR- in the nucleus of neoplastic cells (DAB, ×100); (F) Her2+ in the membrane of neoplastic cells (DAB, ×100).***

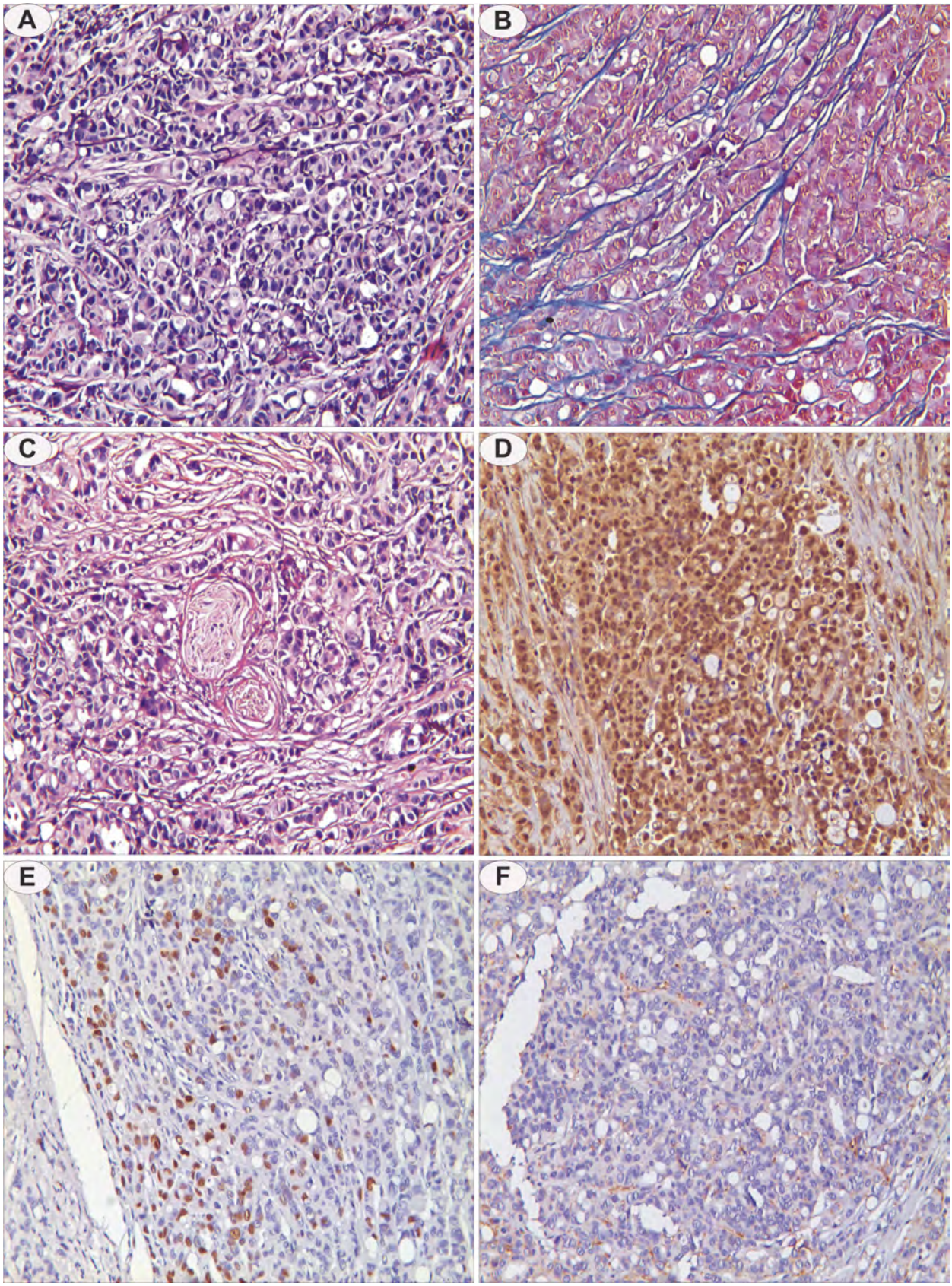

Figure 2 – ***Breast invasive lobular carcinoma – solid type: (A and B) Large solid sheets with little intervening stroma (HE/Masson stain, ×100); (C) Perineural invasion (HE stain, ×100); (D) ER+ in the nucleus of neoplastic cells (DAB, ×100); (E) PR+ in the nucleus of neoplastic cells (DAB, ×100); (F) Her2- in the membrane of neoplastic cells (DAB, ×100).***

Regarding pTNM stage and lymph node status, we noticed a stage II without lymph node metastasis in one case stage III with lymph node involvement in other two cases and in the last case a stage IV with lymph node metastasis. The hormonal receptors and Her2 status in this ILC variant showed reactivity for the ER and PR,

while Her2 immunoreactivity was present only in one case (Figure 2, D–F).

As for the combined receptors status, we found an ER+PR+Her2- immunoprofile in three cases and an ER+PR+Her2+ immunophenotype in one case.

Histiocytoid type was present in four cases with patients' ages being around the general median age at onset. In this ILC variant, the majority of tumor cells had a histiocytoid-like appearance. These presented abundant foamy to granular cytoplasm, round to ovoid, dark to vesicular nuclei, centrally or eccentrically placed with mild variation in size and shape, and small nucleoli which sometimes were obvious (Figure 3, A and B).

The cytoplasm granularity was highlighted by PAS reaction and in two cases with Alcian Blue we could identify intracytoplasmic lumina (Figure 3C).

The neoplastic cells were loosely cohesive proliferating more frequently in a solid pattern and less frequently in a linear and targetoid fashion without desmoplastic reaction. In one case, we noticed a pagetoid extension of tumor cells in the adjacent ducts and in other case a lobular carcinoma *in situ* close to the tumor proliferation.

The tumor grade in three cases was scored as 2 and in one as 1. As for the pTNM stage, we noticed that two cases had a stage II without lymph node metastasis while the other two cases were scored as stage III and presented lymph node involvement. Investigating the hormonal and Her2+ status, we established an ER+PR-Her2+ immunophenotype in two cases and ER-PR-Her2+ immunoprofile in the other two cases (Figure 3, D–F).

Tubulolobular type was recorded in two cases with patients' ages being below the general median age at onset. This ILC variant had a similar infiltrative pattern to that of classic ILC but with some tumor cells organized in small tubules as well as cords (Figure 4, A–C).

Both cases had well differentiated tumors, no lymph node involvement and were diagnosed in less-advanced pTNM stages, respective one case in stage I and the other in stage II. In both cases, the ER and Her2 statuses were positive while PR immunoreactivity was absent.

Therefore, the combined receptor status indicated an ER+PR-Her2+ immunophenotype in both cases (Figure 4, A–C).

Plemorphic type was present in two cases with patients' ages being around the general median age at onset. Histopathologically these tumors were characterized by multifocal nodular aggregates of discohesive, pleomorphic, high-grade tumor cells in dense fibrotic breast parenchyma (Figure 5A).

Also, architectural features similar to the classic type were present, respective single file and targetoid tumor growth patterns. The neoplastic cells demonstrated marked cellular pleomorphism and nuclear atypia.

The nuclei were enlarged (four times the size of a lymphocyte) with greater nuclear irregularity, increased hyperchromasia, prominent nucleoli, increased mitotic activity (Figure 5B).

Typically, tumor cells had moderate-to-abundant eosinophilic, faintly granular cytoplasm, but signet ring cells, plasmacytoid cells and even cells with apocrine differentiation were noticed. Also, in the close proximity of the tumoral proliferations there were present areas of classic or pleomorphic lobular carcinoma *in situ* (Figure 5C).

Perineural invasion, blood and lymphatic vessel invasion were also present in both cases. In one case the tumor differentiation degree was scored as 2, pTNM stage was assed as II, without any detectable lymph node metastasis. The other case was characterized by a grade 3 tumor differentiation, stage III pTNM and lymph node involvement.

The immunoprofile of these tumors showed in one case an ER-PR-Her2+ immunophenotype, while the other presented a triple positive (ER+PR+Her2+) immunoprofile (Figure 5, D–F).

Alveolar type in our casuistry was diagnosed in only one case in a woman of 57-year-old. Microscopically this tumor was composed of cells, which were similar in morphology to those from classic ILC. Most of these cells were light with clear cytoplasm and few had a dark aspect, especially those from the periphery of tumor islands. Their nuclei were large, rounded and with abundant euchromatin.

Characteristically, the neoplastic cells grew in an alveolar pattern, consisting of rounded groups or nests of 20 or more cells, separated by thin bands of fibrous stroma (Figure 6, A and B).

Most of these alveoli were not surrounded by basal lamina (Figure 6C), but they were outlined by elongated fibroblasts or myofibroblasts. This case was scored as 1 for tumor differentiation and as stage II pTNM and the patient did not have lymph node involvement. The combined receptor status was of ER+PR+Her2- immunophenotype (Figure 6, D–F).

Trabecular type was present in a 51-year-old woman. Histopathologically, the tumor was composed of neoplastic cells that resembled those from classic ILC, but they were predominantly arranged in a trabecular growth pattern (Figure 7, A–C).

These infiltrative neoplastic trabeculae consisted of linear bands of two to four cells thick. The tumor-differentiated degree was scored as 2 and the pTNM stage was assessed as stage III. The combined receptor status was of ER+PR-Her2+ immunophenotype (Figure 7, D and F).

Descriptive statistics of the cases identified as non-classical pooled together type revealed a median age of 59 years for this group.

Considering the data grouped for the non-classical types separately, the average ages of these types were of 57±0 (for the alveolar type), 63.25±3.5 (for the solid type), 52±4.24 (for the tubulolobular type), 51±0 (for the trabecular type), 60.5±3.53 (for the pleomorphic type), and 60±1.82 (for the histiocytoid type), and were overall significantly different for each group, $F(5,8)=5.111$, $p=0.021$ (Figure 8).

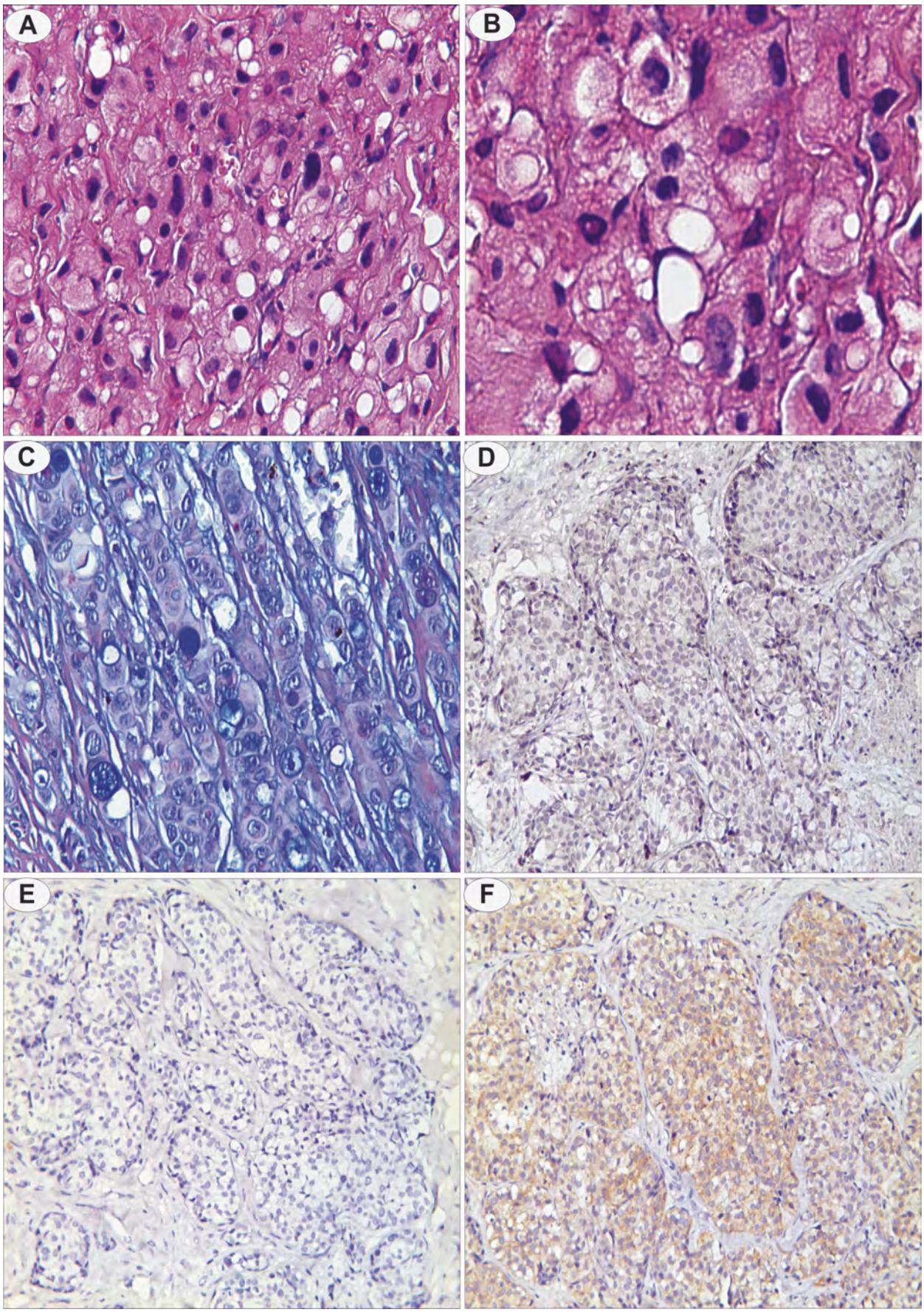

Figure 3 – ***Breast invasive lobular carcinoma – histiocytoid type: (A and B) Tumor cells with histiocytoid-like appearance (HE stain, ×200/×400); (C) Intracytoplasmic lumina identified by Alcian Blue reaction (PAS–Alcian Blue stain, ×200); (D) ER- in the nucleus of neoplastic cells (DAB, ×100); (E) PR- in the nucleus of neoplastic cells (DAB, ×100); (F) Her2+ in the membrane of neoplastic cells (DAB, ×100).***

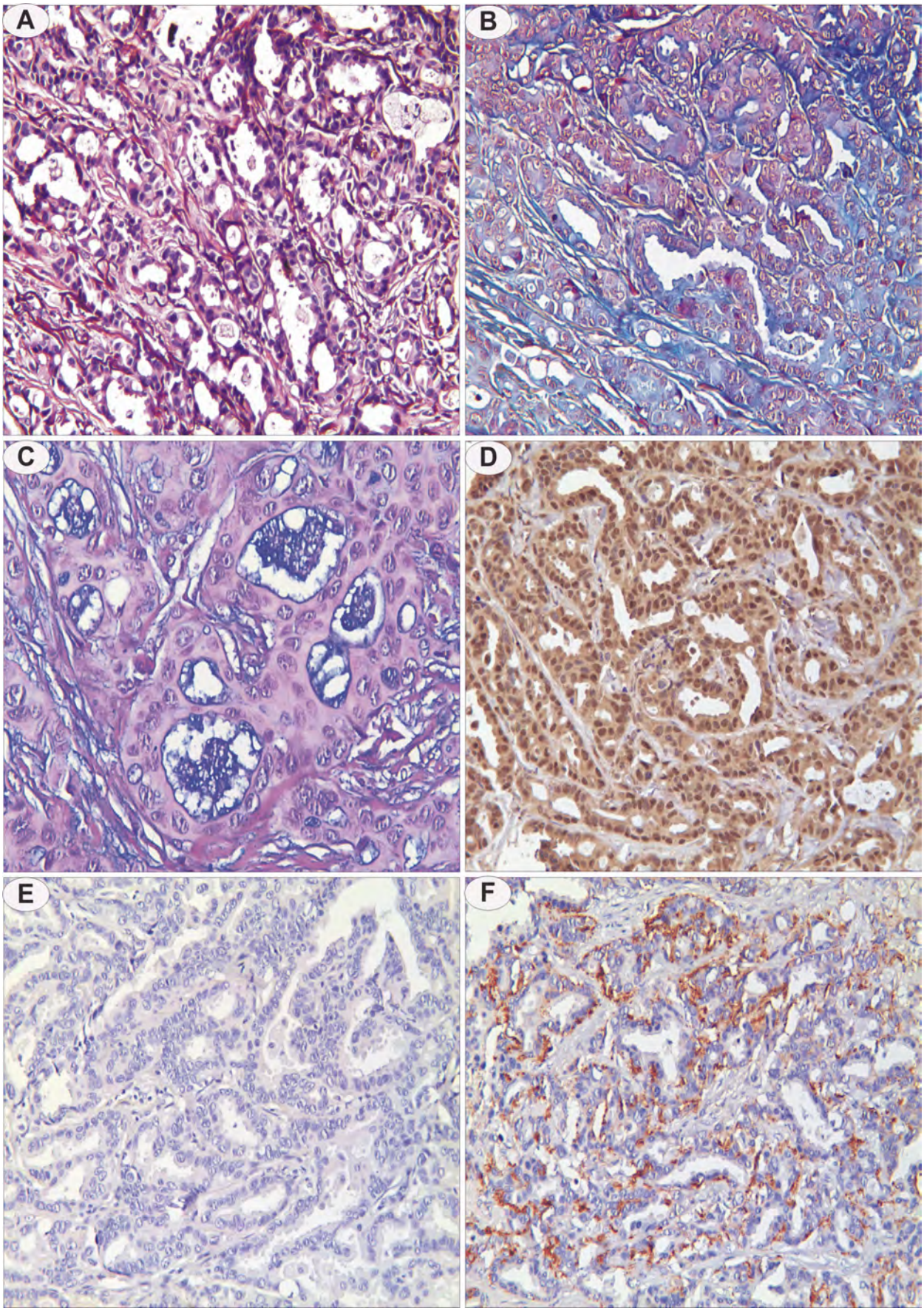

Figure 4 – ***Breast invasive lobular carcinoma – tubulolobular type: (A–C) Tumor cells organized in small tubules as well as cords (HE/Masson/PAS–Alcian Blue stain, ×100/×100/×200); (D) ER+ in the nucleus of neoplastic cells (DAB, ×100); (E) PR- in the nucleus of neoplastic cells (DAB, ×100); (F) Her2+ in the membrane of neoplastic cells (DAB, ×100).***

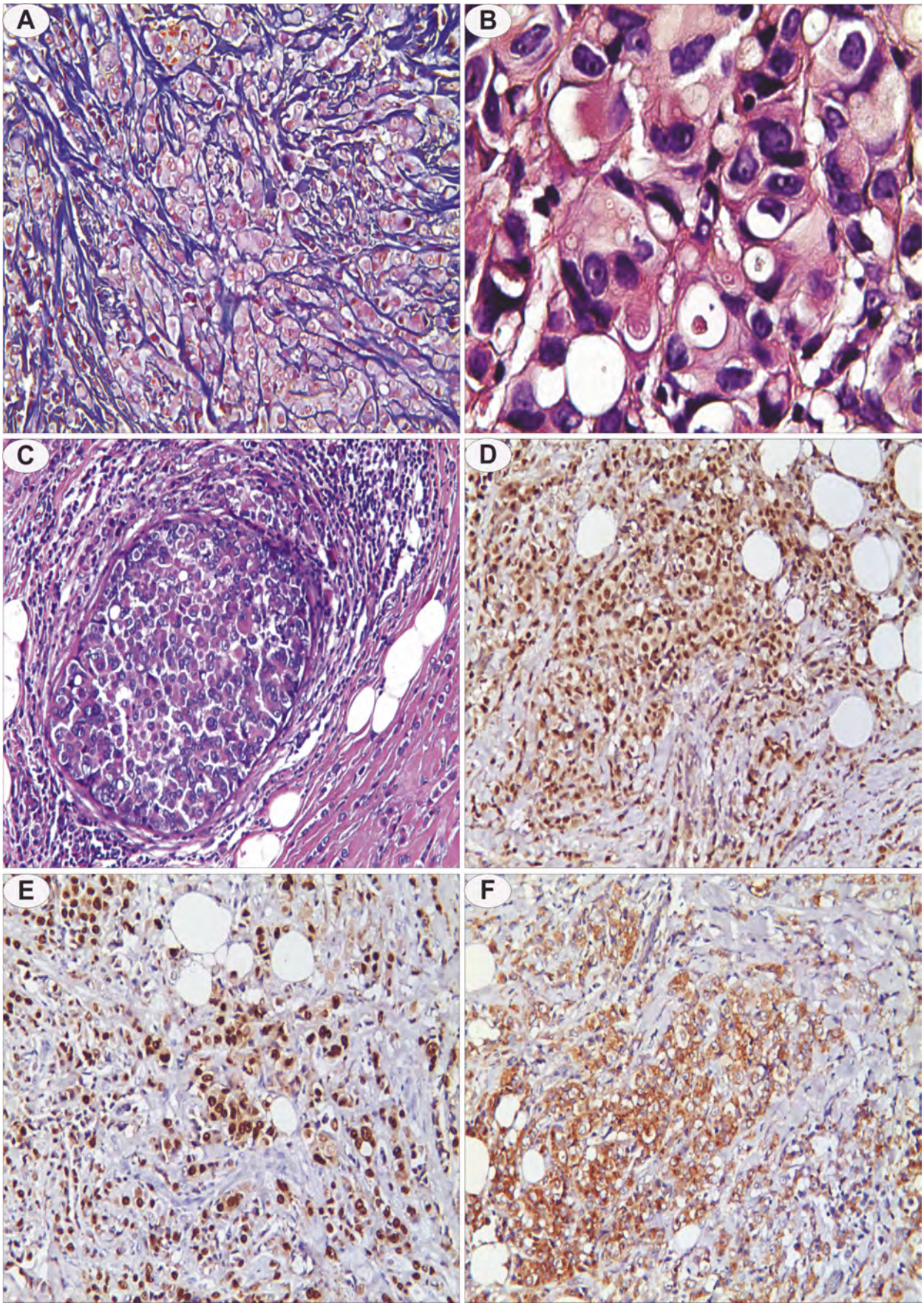

Figure 5 – ***Breast invasive lobular carcinoma – pleomorphic type: (A) Aggregates of discohesive, pleomorphic, high-grade tumor cells in dense fibrotic breast parenchyma (Masson stain, ×100); (B) Greater nuclear irregularity, increased hyperchromasia, prominent nucleoli, increased mitotic activity (HE stain, ×400); (C) Pleomorphic lobular carcinoma in situ (HE stain, ×100); (D) ER+ in the nucleus of neoplastic cells (DAB, ×100); (E) PR+ in the nucleus of neoplastic cells (DAB, ×100); (F) Her2+ in the membrane of neoplastic cells (DAB, ×100).***

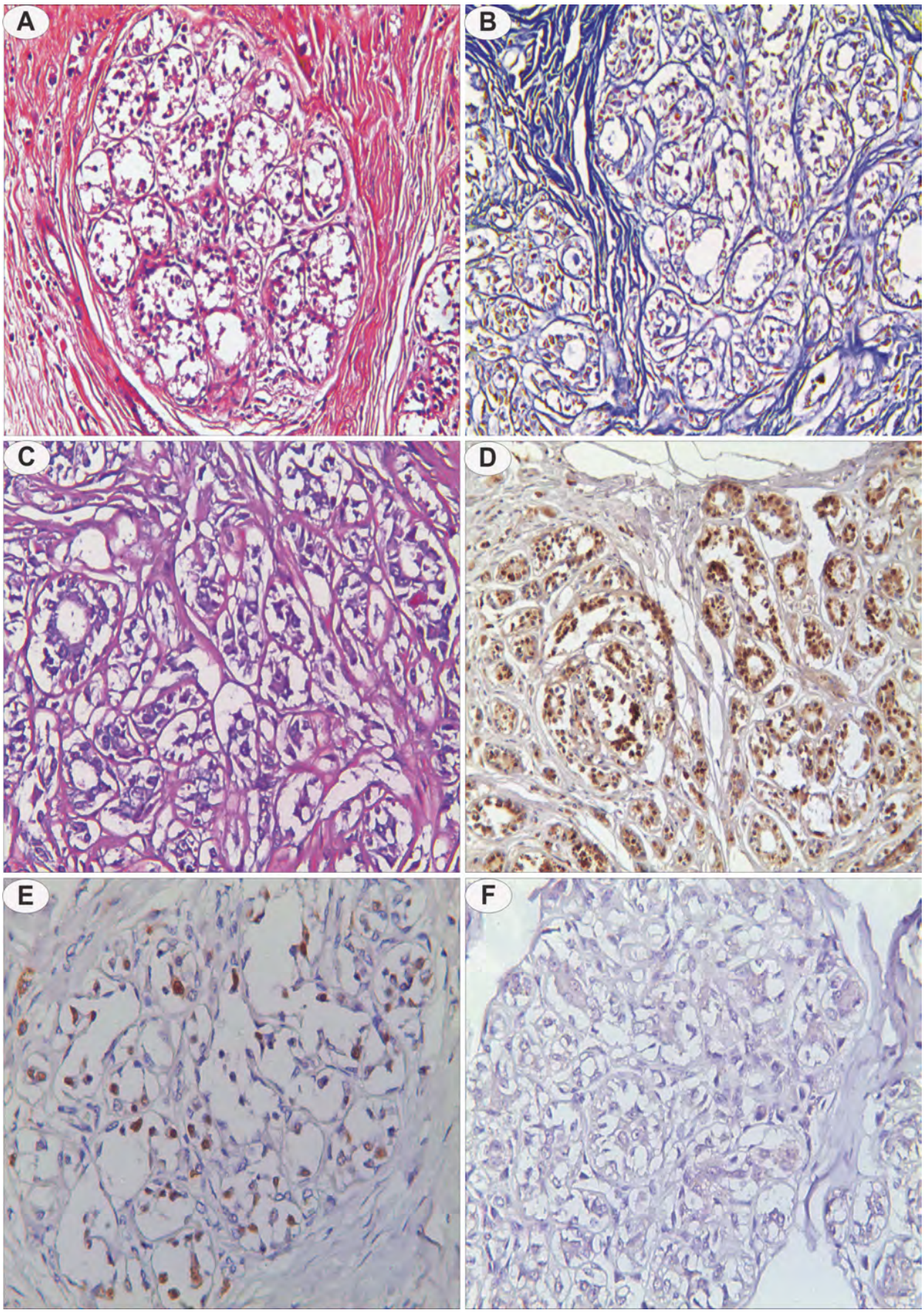

Figure 6 – ***Breast invasive lobular carcinoma – alveolar type: (A–C) Neoplastic cells arranged in an alveolar growth pattern (HE/Masson stain, ×100); (C) Most of these alveoli were not surrounded by basal lamina (PAS–Alcian Blue stain, ×200); (D) ER+ in the nucleus of neoplastic cells (DAB, ×100); (E) PR+ in the nucleus of neoplastic cells (DAB, ×200); (F) Her2- in the membrane of neoplastic cells (DAB, ×200).***

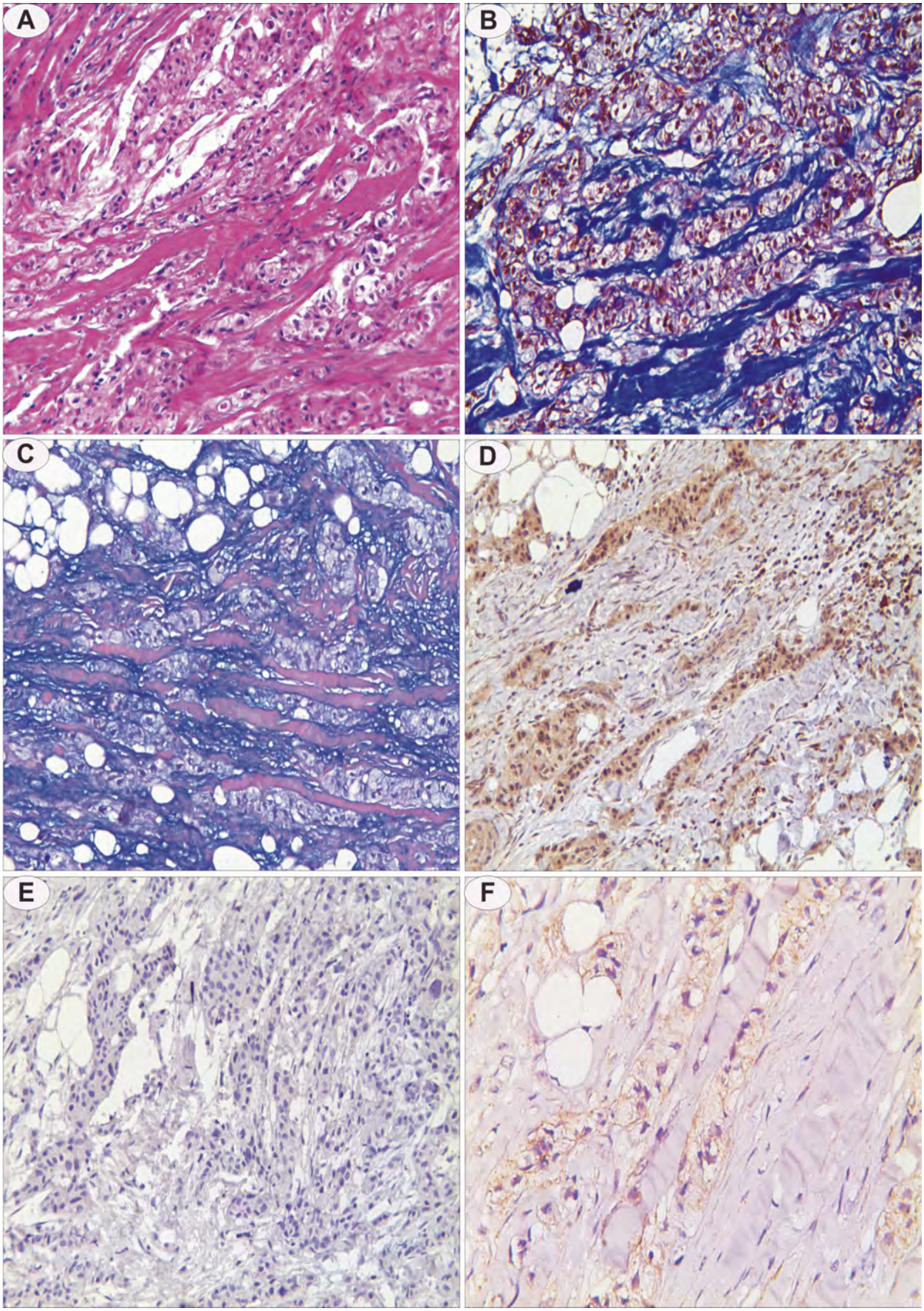

Figure 7 – ***Breast invasive lobular carcinoma – trabecular type: (A–C) Neoplastic cells arranged in a trabecular growth pattern (HE/Masson/PAS–Alcian Blue stain, ×100); (D) ER+ in the nucleus of neoplastic cells (DAB, ×100); (E) PR- in the nucleus of neoplastic cells (DAB, ×100); (F) Her2- in the membrane of neoplastic cells (DAB, ×200).***

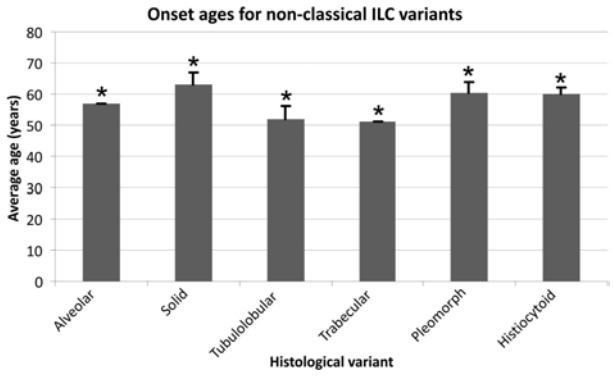

Figure 8 – ***The average ages of different histological variants of non-classical breast invasive lobular carcinoma vary significantly. *Significance on ANOVA testing.***

The percentage of ER+ *vs.* ER- hormonal status did not differ for the groups with ages <59 years and >59 years, $\chi^2(1, N=14)=0.141$, $p=0.707$. There was no difference regarding the distribution of ER status between the tumor grades 1, 2 and 3, $\chi^2(2, N=14)=3.818$, $p=0.148$. There was no difference in the distribution of ER status over the pTNM stages I, II, III and IV, $\chi^2(3, N=14)=1.131$, $p=0.770$. There was no difference in the distribution of ER status over the lymph node invasion status, $\chi^2(1, N=14)=0.424$, $p=0.515$. The distribution of PR+ hormonal status was more frequent among patients with ages >59 years, while the PR- hormonal status was more frequent among patients with ages <59 years, $\chi^2(1, N=14)=4.667$, $p=0.031$. There was no difference in the distribution of PR status between the tumor grades 1, 2 and 3, $\chi^2(2, N=14)=4.286$, $p=0.117$. There was no difference in the distribution of PR status over the pTNM stages I, II, III and IV, $\chi^2(3, N=14)=2.000$, $p=0.572$. No difference was also recorded between PR status and invaded lymph nodes, $\chi^2(1, N=14)=0.286$, $p=0.593$. The percentage of Her2+ *vs.* Her2- status did not differ for the groups with ages <59 years and >59 years, $\chi^2(1, N=14)=0.729$, $p=0.393$. There was no difference in the distribution of Her2 status between the tumor grades 1, 2 and 3, $\chi^2(2, N=14)=2.858$, $p=0.240$. There was no difference in the distribution of Her2 status over the pTNM stages I, II, III and IV, $\chi^2(3, N=14)=3.383$, $p=0.336$. There was no difference in the distribution of HER2 status over the lymph node invasion status, $\chi^2(1, N=14)=0.000$, $p=1.000$.

As the solid and the histiocytoid subtypes were the most frequent, we next looked for differences between the hormonal status and invasion denominators in these two categories. The percentage of ER+ *vs.* ER- hormonal status did not differ for the solid and the histiocytoid subtypes, $\chi^2(1, N=8)=2.667$, $p=0.102$. Most of the PR+ tumors were solid (4 out of 4), while PR- tumors were histiocytoid (3 out of 4), $\chi^2(1, N=8)=4.800$, $p=0.028$. Most of the Her2+ tumors were of the histiocytoid subtypes (4 out of 4), while the solid ones were Her2- (3 out of 4), $\chi^2(1, N=8)=4.800$, $p=0.028$. There was no different lymph node invasion status for these two entities, $\chi^2(1, N=8)=0.533$, $p=0.465$. There was no different distribution for the pTNM pathological staging among them, $\chi^2(2, N=8)=1.333$, $p=0.513$. Also, the tumor grading was not different for these pathological variants, $\chi^2(2, N=8)=3.200$, $p=0.202$.

Next, we compared the different denominators between the overall classical and non-classical groups for both the two age categories <58 years and >58 years. For the <58 years group, there was no difference between the ER expression status for the classical versus non-classical tumor groups, $\chi^2(1, N=11)=0.020$, $p=0.887$. The PR and Her2 hormonal statuses were also not different, $\chi^2(1, N=11)=0.917$ (0.749), $p=0.338$ (0.387). There was no different lymph node invasion status for the two entities, $\chi^2(1, N=11)=0.917$, $p=0.338$. There was no different distribution for the pTNM staging among them, $\chi^2(2, N=11)=4.547$, $p=0.103$. Regarding the tumor grading, grade 1 predominated in classical forms (5 of 5) while grades 1 and 2 were equally distributed for non-classical types, $\chi^2(1, N=11)=3.438$, $p=0.064$. For the >58 years group, there was no difference between the ER expression status for the classical *vs.* non-classical tumor groups, $\chi^2(1, N=14)=1.750$, $p=0.186$. The PR and Her2 hormonal statuses were also not different, $\chi^2(1, N=14)=0.141$ (2.941), $p=0.707$ (0.086). There was no different lymph node invasion status for the two entities, $\chi^2(1, N=14)=0.117$, $p=0.733$. There was no different distribution for the pTNM staging among them, $\chi^2(2, N=14)=4.764$, $p=0.092$. Finally, there was no difference between grades 1, 2 and 3 distribution for the two groups, $\chi^2(2, N=14)=3.111$, $p=0.211$.

Discussion

According to *Surveillance Epidemiology and End Results Program* (SEER) data, the incidence of breast tumors with lobular component raised from 9.5% in 1987 to 15.6% in 1999, mainly in post-menopausal women in their 50–59-year-old [3, 5]. More recent data showed a decrease in incidence of invasive breast cancers beginning from 2002 [38–40]. Eheman *et al.* reported for 2003 the largest percentual decline for ILC with an 8.5% drop in age-adjusted rates for that year.

This variant of invasive breast cancers was first described by Foote FW and Stewart FW in 1941 [41]. Since then, over time, many histological studies had proved the morphological heterogeneity of ILC. According to the *World Health Organization Histological Typing of Breast Tumors*, second edition, the classical ILC histological form is defined as follows: „the cells grow typically in a single-file, linear arrangement, or appear individually embedded in fibrous tissue. Infiltrating cells are often arranged concentrically around ducts, in a target-like pattern" [42]. Besides this classical form several distinct variants of ILC were reported, recognized either by their characteristic architectural pattern, namely alveolar [10, 43, 44], trabecular [10], solid [9, 45] or tubulolobular [46], or by cytopathological features, signet ring cells [47], apocrine [8, 12, 48], histiocytoid [12, 49–51] and pleomorphic [51–55]. To diagnose such an ILC subtype, this particular feature must comprise more than 50% of the tumor [52]. Usually these variant patterns exist only in a modest proportion of the whole tumor volume and even more,

there can be more than one such single particular pattern. Moreover, both classical form and the other histological variants may coexist in the same specimen with *in situ* or invasive ductal carcinoma. In such conditions, the correct histopathological typing of breast carcinomas may be challenging.

In our study, the non-classical ILC type represented 54% with the solid and histiocytoid subtypes as the most frequently encountered, each one with 16%. The other variants were diagnosed in a limited number of cases: two cases of tubulolobular, two cases of pleomorphic, and one case of alveolar and trabecular subtypes. The classical ILC type was diagnosed in 44% of invasive lobular breast cancer cases. Reviewing the literature data we found that Orvieto E *et al.*, investigating 530 cases of breast ILC (retrieved between 1994 and 2001), established that 43% of the cases belonged to non-classic variants of ILC, with a relative prevalence of the alveolar (19%) and solid (11%) subtypes [4]. Rakha EA *et al.* [6], on a casuistry of 544 ILC cases, established that the most frequently found subtype was the classical one with 55%, followed by mixed lobular subtypes with 34%, solid with 5%, tubulolobular 4% and alveolar with 2%. Recently, Iorfida M *et al.*, studding 981 breast ILC diagnosed at the *European Institute of Oncology* between 1994 and 2005, concluded that 55.8% were of classic type, 14.9% of alveolar type, 14.8% of mixed non-classic, 10.6% of solid type, and 3.9% of trabecular type [56].

The majority of studies revealed so far that this form of breast cancer had a specific clinicopathological profile. It appears that the classic ILC type: (1) occurs in middle-aged or older patients (peak incidence for the 40–70-year-old group) [5]; (2) has an increased propensity for multifocality and multicentricity; (3) has a higher risk of bilateralisation; (4) usually grows as a larger tumor; (5) has a lower histological grading (I/II) [16]; and (6) in the vast majority of the cases these are classified as part of the "luminal" molecular subgroup (ER+PR+Her2-) [1, 57, 58], suggesting its origin in more differentiated luminal cells [59]. Also, it seems to have a higher rate of multiple metastases [17], and an increased propensity to involve the bones, gastro-intestinal tract, uterus, meninges, ovary, and serosal cavities [1, 34, 60, 61]. Moreover, some long-term follow-up studies have shown a trend to later locoregional recurrences [21, 22]. Data regarding breast ILC prognosis are controversial with some reports establishing a worse outcome [62, 63], but other with no significant differences than invasive ductal carcinoma [14, 19, 27, 64–66], and finally other authors reported a better prognosis [31, 54, 58, 67–70]. In addition, the ILC seems to be less responsive to neo-adjuvant and adjuvant chemotherapy [21, 24, 28, 31, 32, 71, 72], but by being more often HR-positive are more susceptible to adjuvant hormonal therapy [32, 68].

More of these clinicopathological characteristics of the classic ILC type have been confirmed by us. So, we have established that this invasive breast cancer had a median onset of 58-year-old, a prevalent grade 1 as tumor differentiation (63.63%), more than 90% being diagnosed in stage I/II pTNM more often without metastasis (63.63%), and 91% of them were ER+, 45% PR+ and 36% Her2+. The most frequent encountered combined receptor status was ER+PR+Her2- (36%), followed by the ER+PR-Her2+ immunoprofile (27%). Overall, the statistical analysis proved that among patients with classical breast ILC there was no significant difference regarding the distribution of hormonal (ER, PR) and Her2 receptors status in relation with the major clinico-morphological investigated parameters. However, our investigation revealed that the PR- hormonal status was more frequent among patients with ages <58 years, while the PR+ hormonal status was more frequent among patients with ages >58 years and with lymph node invasion. The non-classic ILC had a median onset of 59-year-old, with the predominance of grade 2 tumor differentiation (50%), stage II/III pTNM (each one with 43%), and 50% with lymph node involvement. Their immunoprofile showed that 78.57% were ER+, 71.42% Her2+ and 50% of these cases presented PR reactivity. When we examined the combined receptor status we found that ER+PR-Her2+ and ER+PR+Her2- immunoprofiles were most frequently encountered (each one with 28.57%). Similar to the classical breast ILC group, patients from the non-classical ILC group do not show significant differences regarding the distribution of hormonal (ER, PR) and Her2 receptors status in relation to the major clinico-morphological investigated parameters. Only for the hormonal PR receptor status, we found that a positive immunoprofile was more frequent among patients with ages >59 years and with a solid histological variant, while the PR- status was more frequent among patients with ages <59 years and with a histiocytoid histological variant. Also, a significant difference was noted in the Her2 receptor status according to the histological variant, with a positive reaction especially in the histiocytoid subtype, while patients with solid variant were predominant negative to this marker. Moreover, when we compared the different denominators between the overall classical and non-classical groups for both the two age categories (<58 years and >58 years) we did not find any significant statistical differences.

Comparing classic and non-classic breast ILC, Orvieto E *et al.* found that patients with the non-classic type had an increased number of distant metastases and reduced disease-free survivals and overall survivals than those diagnosed with classic ILC [4]. The less favorable prognosis of some histopathological variants of ILC was previously identified by other authors, although these observations were based on limited number of cases [55, 73]. In the same way, du Toit RS *et al.*, investigating five distinct subtypes of ILC (classic, tubulolobular, solid, alveolar, and mixed), showed a significant difference of the disease-free survivals and overall survivals between the tubulolobular and the solid variants, with the former being relatively more indolent than the latter [67]. On the other hand, Tot T [81] found on a univariate analysis that the solid subtype correlated with shortened disease-free survival and overall survival, and the alveolar subtype with reduced disease-free survival, these associations did not attain statistical significance on multivariate analysis, most probable to

the low number of cases from these ILC subtypes. On the contrary, in the study conducted by Iorfida M *et al.* a statistically significant difference in the outcome was observed on a multivariate analysis, for patients with solid and mixed non-classic ILC *vs.* patients with classical ILC [56]. In addition, Rakha EA *et al.* investigating as Toit *et al.* five distinct subtypes of ILC (classic, tubulolobular, solid, alveolar, and mixed) established an association between the histological subtype and mitotic counts (with higher scores in solid and mixed variants and low in tubulolobular and classical types), tubule formation and pleomorphism [6].

More recent data indicate the pleomorphic variant as a particularly aggressive subtype of ILC especially due to more pronounced cytologic changes, predisposition to peritumoral vascular invasion, a lower rate of expression of hormone receptor status, and a higher rate of overexpression/amplification of the HER2/neu gene [4, 26, 54]. While Buchanan CL *et al.* [75] found for pleomorphic ILC a median age at diagnosis of 59 years and a median tumor size of 2 cm, Monhollen L *et al.* established for this variant of ILC a more increased median age (61 years), with 75% of patients being in postmenopausal status [76]. In addition, Buchanan CL *et al.* showed that pleomorphic ILC type were larger and were more likely to develop tumor metastases compared to ductal carcinoma and classical ILC [75]. The preferential sites of metastasis in this type of ILC were bone, liver, lung and peritoneum after a mean follow-up of 3.8 years. Also, compared with conventional ILC, Buchanan CL *et al.* [75] and Eusebi V *et al.* [55] established that pleomorphic ILC had a significantly higher rate of recurrence [75]. Moreover Monhollen L *et al.* showed that pleomorphic ILC is a unique type of breast cancer, with mixed lobular and ductal clinico-pathological characteristics. The advocates of lobular carcinoma resemblance are the morphology, E-cadherin reaction and the lack of basal keratins, while for ductal carcinoma resemblance were peculiar the aggressive clinical behavior, triple negative receptor profile and Her2+ reactions, and an increased p53 expression. Regarding the prognosis of pleomorphic ILC, Bentz JS *et al.* [77] showed a poorer outcome than for low-grade ductal carcinoma, but a similar outcome when compared with high-grade ductal carcinoma. The 5-year recurrence-free survivals and overall survivals were shorter than classical ILC, and almost similar to that expected in ductal carcinoma [55, 76].

These findings emphasize that the histopathologic subtyping of ILC is clinically useful, and provides additional information to direct and individualized treatment decisions, considering non-classic ILC type as a particularly aggressive subtype.

Conclusions

In our casuistry, the non-classical ILC type was prevalent with solid and histiocytoid as the most frequently encountered subtypes. When compared to classical ILC variant, it was diagnosed in more aged patients, with a more advanced tumor degree differentiation and pTNM stage, with 50% lymph node involvement and no significant differences in terms of ER/PR/Her2 immunoprofile. Statistically we noticed that in classical ILC the PR+ hormonal status was more frequent among patients with ages >58 years and with lymph node invasion, while for the non-classical ILC type this immunoprofile was more prevalent among patients with ages >59 years and with a solid histological variant.

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