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Invasive Micropapillary Carcinoma of the Breast: Comparison of Clinical, Epidemiological, Anatomopathological and Therapeutic Features with Infiltrating Carcinoma of Non-Specific Type

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Abstract **Original Research Article**

Invasive micropapillary carcinoma (IMCC) is a rare histological subtype of invasive breast cancer, its frequency ranges from 1.0 to 8.4% of all breast cancer cases. It is identified as a particularly aggressive tumor since frequent invasion of vessels, skin and lymph nodes is often reported. The aim of the work is to describe and compare the epidemiological, clinical, anatomopathological and molecular aspects of CMPI compared to CINS. Compare the overall survival of the two groups in order to identify the prognostic factors for CMPI. This is a retrospective, descriptive and analytical study spread over 6 years from January 2015 to December 2020, involving all cases of CMPI and CINS of the breast collected at the Obstetrics and Gynecology department of the Maternity and Neonatology Center of Monastir. The frequency found was 5.5% for CMPI and 72.69% for CINS. In our series we found the average age to be more advanced in CINS compared to CMPI without having a statistically significant difference (p=0.49). CMPI tends to be slightly larger than CINS with an average size of 3.7 compared to 3 for CINS. The right breast was the predominant tumor site for the 2 types of cancer p=0.71. CMPI presents a higher frequency of locoregional ADP and vascular emboli with p=0.001. Distant metastases were more frequent in CINS but without having a statistically significant difference. The overall survival of CMPI is 76% versus 86.4%. % of CINS. CMPI represents a particular variety of breast carcinomas; in this study we tried to dissect its different epidemiological, clinical, radiological and therapeutic characteristics which were largely in agreement with the literature.

Keywords: Invasive micropapillary carcinoma (IMCC), Breast cancer, Epidemiology, Prognosis, Molecular characteristics.

INTRODUCTION

Invasive micropapillary carcinoma (IMCC) is a rare histological subtype of invasive breast cancer, its frequency ranges from 1.0 to 8.4% of all breast cancer cases [1]. It is a variant characterized histologically by a predominant micropapillary architecture [2].

It is characterized by the presence of small clusters and nests of tumor cells arranged within well-defined clear spaces, resembling lymphatic vessels [2].

CMPI demonstrates significant genomic heterogeneity with multiple chromosomal aberrations, and tends to be genetically more complex than nonspecific infiltrating carcinoma (INSC) [3].

However, their histological singularity and aggressive behavior make them a very particular subtype which has in recent years given rise to a series of analyzes intended to better understand their pathophysiology.

It is identified as a particularly aggressive tumor since frequent invasion of vessels, skin and lymph nodes is often reported.

Despite a prognosis that could be more unfavorable, the low incidence of CMPI has made it difficult to adopt a specific treatment. The latter remains the same as that for an invasive carcinoma of non-specific type which represents the most common type [4].

However, the characteristics that distinguish CMPI from CINS must be considered in order to properly manage treatment and improve prognosis.

To better understand these characteristics, our current study was planned with a group of patients treated in the obstetrics and gynecology department at the Monastir maternity and neonatology center over a period of 6 years.

The present study aims to compare CMPI and CINS. We will compare the epidemiological, clinical, anatomo-pathological and molecular aspects of these two groups. Also compare the overall survival of the two groups to identify prognostic factors.

METHODS

Type and framework of the study:

This is a retrospective cohort study carried out over 6 years: from January 2015 to December 2020. All patients hospitalized for breast cancer of the CMPI or CINS type in the gynecology and obstetrics department of the maternity and neonatology center of Monastir were were included in this work.

Study Population:

Inclusion Criteria:

Female Gender

Micropapillary carcinoma and non-specific invasive carcinoma diagnosed on a tissue sample: micro-biopsy, lumpectomy or mastectomy and had surgical treatment. Diagnosis carried out between January 2015 and December 2020

Non-Inclusion Criteria:

- Carcinomas in situ
- Surgical treatment not done
- Carrier of synchronous cancer
- Died or lost to follow-up before starting any treatment
- Unusable files: lack of detail in the observation
- Discrepant histology between biopsy and surgical specimen

Definition of variables and data source:

The variables studied were:

Epidemiological characteristics: age of the patient at the time of diagnosis, age of the patient at menarche, parity, age at first pregnancy, duration of breastfeeding, etc.

Clinical characteristics: time and reason for consultation, clinical examination data, characteristics of the breast nodule.

Radiological diagnosis criteria for breast cancer: The analysis of echo-mammography data is carried out according to the recommendations of the 5th Edition of the American College of Radiology (ACR) of the Breast Imaging Reporting and Data System (BIRADS).

Histological criteria for the diagnosed tumor:

The criteria studied are mainly the criteria necessary to establish the prognosis of the patient: The number of lesions, multifocality, histological tumor size, SBR tumor grade, the presence of vascular emboli, perineural sheathing, the presence of lymph node invasion, the status of hormonal receptors (R0: estrogen receptor, RP: progesterone receptor), HER-2 receptor status; Ki 67.

Therapeutic conduct: this was discussed with multidisciplinary staff weekly magazines which bring together different specialties (gynecology, radiology, oncology and anatomopathology). Surgical treatment: radical/conservative/salvage, radiotherapy, chemotherapy, hormonal therapy, targeted therapy.

Data collection was done using an anonymous computerized form by consulting the medical files, the radiological and pathological reports of the patients as well as the follow-up at the gynecology and oncology outpatient consultation.

Data entry and analysis was done using SPSS version 2020 software. The qualitative variables were described by their corresponding numbers and percentages and the quantitative variables by their means and standard deviations.

The comparison of the different epidemiological, clinical, radiological and prognostic characteristics of patients according to the type of cancer (CMPI or CINS) were made using the Student's t test for the comparison of means and the Pearson chi-square test or the Fisher's bilateral exact.

Survival rate was estimated using the Kaplan Meier method. The statistical significance threshold was set at 0.05.

RESULT

In total, 25 cases of CMPI were collected, or 5.5% of all breast cancers treated in our center. CINS represented 72.68% of breast cancers. The median age of the population was 49.29 in the CMI group versus 51 in the CINS group; p=0.49. CMPI tends to be slightly larger than CINS with a median tumor size of 3.7 compared to 3 for CINS; P=0.665.

The right breast was the predominant tumor site for both types of cancer (p=0.71). The presence of locoregional lymphadenopathy was significantly different. CMPI presents a higher frequency of lymph node invasion than CINS with p = 0.001. Distant metastases were more frequent in CINS but without a statistically significant difference.

The epidemiological and clinical characteristics of the cohort are summarized in Table 1. Concerning the anatomopathological characteristics: Vascular emboli were more frequent in CMPI 44% compared to 13.86% in CINS (P=0.001).

The majority of CMPIs in this series were high grade, 15% of which were SBR grade 2 and 36% SBR grade 3. The same in CINS, 50% of cases were SBR grade 2 and 29% of cases were SBR grade. 3; P=0.281.

Immunohistochemically we found that CMPI has a higher frequency of hormonal receptors (84%) than CINS (78.27) without the difference being statistically significant (P=0.436).

The Luminal Classes were the majority classes at the CMPI, the Luminal A class represented 56.5% and Luminal B 30.4%, the others Classes were infrequent. The same for the CINS, the luminal classes represented the majority of the classes (luminal A 69.7% and Luminal B 10%); P=0.06. All these factors were summarized in Table 2.

As for the therapeutic aspect, we opted more for radical treatment than conservative treatment for the 2 types of tumors. We did not find a statistically significant difference between the two (P at 0.516). Concerning the adjunct treatment of CMPI, we used more multimodal treatment compared to CINS with non-significant associations.

Prognostic factors negatively influencing CMPI OS detected in our series were essentially exposure to irradiation, the negativity of hormone receptors, and the non-use of chemotherapy.

The overall 5-year survival rate of patients in our study was 85.6%. The one relating to CMPI was 76% (6 deaths) and that of CINS was 86.4% (45 deaths), (curve n°1).

The average survival of patients with CMPI and a large tumor between 0 and 5 cm (n=16) was estimated at 35.4 months at a 95% CI [18.4-52.3]. The survival rate for this category of patients at 30 months was 60%.

The average survival of patients with CINS and a large tumor between 0 and 5 cm (n=209) was estimated at 36.6 months at a 95% CI [28.6-44.6]. The survival rate for this category of patients at 30 months was 55%. The overall survival rate of CINS was better than that of CMPI for a tumor size less than 5 cm (P=0.045). According to the subgroup analysis including lymph node status and the presence of metastases, we did not find a significant difference between the two types of tumors in terms of OS.

Table 1: Comparison of the epidemiological and clinical characteristics of CMPI and CINS

	CINS	CMPI	
Number	330 (72.68%)	25 (5.5%)	
	CINS	CMPI	P-value
Average age	51 years old	49.29	0.49
	CINS	CMPI	P-value
Family history of neoplasia NB TOT = 354 CMPI = 25 CINS = 329			0.408
No	192(58.35%)	18 (72%)	
Yes	118(35.86%)	6 (24%)	
Not specified	19 (5.7%)	1(4%)	
Personal history of Neoplasia NB TOT=348 CMPI=25 CINS=323			0.206
No	302(93.48%)	23(92%)	
Contralateral breast	1(0.309%)	1 (4%)	
Ovary	1(0.309%)	0	
Others	4 (1.23%)	0	
Unspecified	15(4.6%)	1(4%)	
	CINS	CMPI	P-value
Taking OP pills NB TOT=215			0.324

CMPI=21 CINS=194			
No	164(84.53%)	20 (95%)	
Yes	30(15.46%)	1 (5%)	
	CINS	CMPI	P-value
Tumor size NB TOT= 293 CMPI=21 CINS=272			0.665
Midsized	3cm	3.7cm	
0-5cm	209 (76.83%)	16(76.19%)	
6-10cm	63 (23.16%)	5(23.80%)	
	CINS	CMPI	P-value
Tumor site NB TOT=215 CMPI=25 CINS= 319			0.713
Right breast	169(52.97%)	14 (56%)	
Left breast	144(45.14%)	10 (40%)	
Bilateral	6(1.8%)	1(4%)	
	CINS	CMPI	P-value
ACR NB TOT=312 CMPI=23 CINS=289			0.5
4	86(29.75%)	3(13.1%)	
5	203 (70.24%)	20 (86.9%)	
	CINS	CMPI	P-value
T: NB TOT =344 CMPI=25 CINS= 319			0.474
Texas	4 (1.25%)	1(4%)	
T1	74 (23.2%)	7 (28%)	
T2	132 (41.4%)	13 (52%)	
T3	44 (13.8%)	2(8%)	
T4	65(20.35%)	2(8%)	
NOT : NB TOT=347 CMPI=25 CINS=322			0.001
Nx	1 (0.3%)	0	
N0	226(70.2%)	6 (24%)	
N1	68(21.1%)	13(52%)	
N2	20(6.2%)	2 (8%)	
N3	7(2.2%)	4(16%)	
M: NB TOT=347 CMPI=25 CINS=322			0.896
Mx	3(0.95%)	0	
M0	299(92.85%)	24(96%)	
M1	20(6.2%)	1(4%)	

Table 2: Comparison of histological and immunohistochemical characteristics of CMPI and CINS

	CINS	CMPI	P-value
*Capsular breakage NB TOT=112 CMPI=20 CINS=92			0.586
Yes	25(27.18%)	4(20%)	
No	67(72.82%)	16(80%)	
*Vascular emboli NB TOT=292 CMPI=25 CINS=267			0.001
Here	37(13.86%)	11 (44%)	
Absent	230(68.14%)	14 (56%)	
*SBR grade NB TOT=327 CMPI=25 CINS=302			0.281
SBR1	62(20.5%)	1(4%)	
SBR2	151(50%)	15 (60%)	
SBR3	89(29.5%)	9(36%)	
	CINS	CMPI	P-value
*HR NB TOT=347 CMPI=25 CINS=322			0.436
Positives	252(78.27%)	21(84%)	
Negatives	70(21.73%)	4(16%)	
*OR NB TOT=317 CMPI=25 CINS=292			0.582
Positives	232(79.45%)	20(80%)	
Negatives	60(20.54%)	5(20%)	
*PR NB TOT=315 CMPI=25 CINS=290			1
Positives	198(68.3%)	16(64%)	
Negatives	92(31.7%)	9(36%)	
*KI67 NB TOT=151 CMPI=17 CINS=134			0.22
Down	17(12.7%)	0	
Pupil	117(87.3%)	17(100%)	
*HER2 new NB TOT=344 CMPI=25 CINS=319			0.58
0	257(80.6%)	16(64%)	
+1	38(11.9%)	1(4%)	
+2	2(0.6%)	1(4%)	
+3	22(6.9%)	7(28%)	

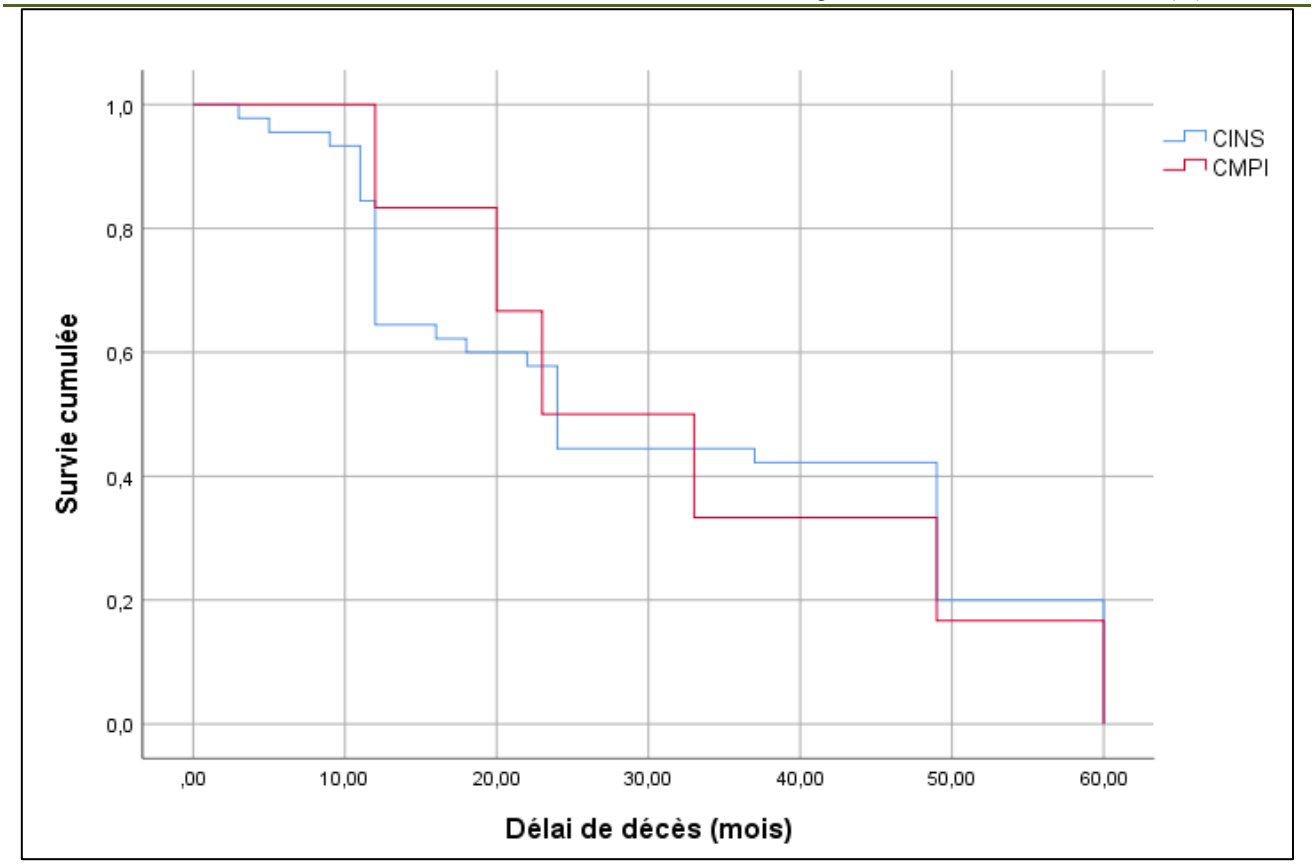

Figure 1: Overall survival curve for CMPI and CINS

DISCUSSION

Invasive micropapillary carcinoma (IMCC) is a relatively rare histological type of invasive breast cancer, accounting for 1.0 to 8.4% of all breast cancer cases [1, 5].

As for non-specific infiltrating carcinoma, it represents the majority of cases of breast cancer with a frequency of 80% of all breast cancers [6, 7]. In our series the frequency of CMPI is 5.5%.

The age of diagnosis is between 50 and 62 years old [8] but this is not specific to micropapillary carcinoma and there is not a significant difference between the two types of cancer in terms of average age. As for the median age of CMPI was 49.29 years and 51 years for CINS.

Clinically, our series was in agreement with the literature in the sense that palpation of a nodule for CMPI was the most common reason (68% of cases). Mastodynia occupies 2nd place with a percentage of 16%.

Likewise for CINS the most frequent reason for consultation was the palpation of a nodule with 68.7%.

In a study carried out by Hammadi et Al concerning 7 patients: 57% of them presented a CMPI in the left breast [9]. In our series the tumor was preferentially located in the right breast.

In a study done by Yang Li and colleagues in 2016, the average size of CMPI found ranged from 1.3 to 3.9 cm but there was not a significant difference between CMPI and CINS [8].

According to Han *et al*., the average size was 34.44±25.68 mm, with a minimum of 13.2 mm and a maximum of 85.4 mm [10].

In our series the difference in size was not significant, the average size of the CMPI was 3.7 which tends to be slightly larger than the CINS.

Radiologically, all aspects found are suggestive of malignancy and are not distinct from those found in CINS.

Moving on to the diagnosis, that of CMPI can be suspected on cytological examination. We generally find cohesive atypical cells taking a pseudo-papillary arrangement and sometimes bathing in a mucoid background [2, 11].

The definitive diagnosis is essentially based on the anatomopathological study of the tumor specimen.

However there is not a significant difference between CMPI and CINS in terms of SBR grading with a P value of 0.281. This result was consistent with the literature, in particular with a comparative study carried out by A. Hashmi *et al*., in 2018 carried out on 1951 cases which did not show a significant association between the two groups [12].

Lymph node involvement according to several studies [13-15] observed what regardless of the size of the tumor and the fact of having a micropapillary contingent, this is associated with greater metastatic lymph node invasion than CINS [3].

Li *et al*., [16] found that CMPI has more pT3 and pT4 stage with P at 0.044 when comparing it with CINS. In our study population the majority of cases are in pT2 (52%) and there is not a significant difference between the 2 groups.

With a pure or mixed mode of presentation, micropapillary carcinoma is characterized by frequent lymphatic diffusion [14] with a very high incidence of lymph node metastasis reaching 95% [17].

According to the study by Li *et al*., [16] CMPI has a higher percentage of N+ with a P value < 0.001.

In our series we found a significant frequency of lymphatic invasion. The N1 stage was in the majority and the difference with CINS is there with a P value of 0.001.

This significant lymphotropism has led some authors to suggest not recommending the sentinel lymph node technique in patients with such histological type [2, 17, 15].

Several studies have shown greater lymphovascular invasion in IMPCs. The presence of a micropapillary component may be predictive of greater lymphovascular invasion [18].

Our study showed a significant difference in favor of CMPI which tends to have vascular emboli more than CINS (P at 0.001).

As for the peri-nervous sheath, there is no significant difference between the two types of breast carcinomas.

X. Guan in his study carried out in 2020 comparing 1231 cases of CINS against 130 of CMPI did not show a difference between the two in terms of peri-nervous sheathing with P value at 0.504 [6].

As for the hormonal receptors, the study by Chen *et al*., [1] revealed that the positivity rate of ER and RP was 88.0% and 75.7%, respectively, significantly higher than that of CINS.

Another study by A. Hashmi *et al*., [12] revealed higher hormone receptors compared to non-specific type invasive carcinoma. HR positivity was present in 87% of CMPI cases, while only 60% of CINS.

One of the studies also indicated that high HR positivity in invasive micropapillary carcinomas is advantageous in terms of survival and attributable to increased life expectancy in female patients.

Therefore, these features suggest a good prognosis in patients with CMPI compared to CINS [19].

Most studies were in agreement with these results [20, 21]. Our series showed a high HR rate of 84% of cases. Estrogen receptors were positive in 80% of cases and progestin receptors were positive in 64% of cases.

HR positivity was higher for CMPI than for CINS without noting a statistically significant difference.

HER2 neu positivity was noted in 60% of cases of CMPI in a study by A. Hashmi [12]. According to the literature, CMPI immunoreactivity for c-erbB-2 was in the range of 36 to 100% [21, 22].

In our series, 36% of cases have overexpression of HER 2 and there is not a significant difference between CMPI and CINS in this sense. This result is in agreement with the study of Hashmi et Al who did not show a significant association with a P value of 0.207.

On the therapeutic side, conservative treatment was practiced in 4 patients in our series, i.e. 16% of cases, which is slightly lower than CINS where conservative treatment is more commonly used. This finding was also found in the study by Chen *et al*., [1] 54.1% vs 59.9% at CINS.

Because of his aggressiveness, Chen and colleagues opted for radical surgery rather than simple conservative treatment [1].

The use of chemotherapy was noted in 88% of cases in our study. The percentages of patients who used chemotherapy were different between the two types of tumors, which was in agreement with the study by Chen *et al*., [1]. The latter found a significant difference between the two groups of neoplasia with 53.9% of patients with CMPI having recourse to chemotherapy compared to 45.6% of CINS patients.

In the study by Chetibi *et al*., seventy-five patients (91.5%) benefited from FAC, AC and taxotere type chemotherapy [23].

In a study done by C.kaya [24], 59.6% of patients had hormonal therapy, a percentage which is

close to our study; or 56% of patients, mainly based on anti-estrogens.

The use of Herceptin was observed in 8 patients or 32%, a percentage which is higher compared to that of CINS without having a statistically significant difference (P at 0.092).

A study done by Jeong Il Yu *et al*., [25] in 2015 showed use of Herceptin in around 44.2% of CMPI cases compared to 47.5% of CINS cases.

To date, no study has specifically aimed to determine the value of radiotherapy in patients with CMPI.

In our series, curative radiotherapy was used in 80% of cases. The total irradiation dose varies between 52.2 and 66.6 gy. Comparing it with CINS we did not find a significant difference between the two.

On an evolutionary level, CMPI of the breast is characterized by its loco-regional aggressiveness; this is manifested by: Frequent vascular invasion [26], lymph node metastases, local recurrence which can be observed in up to 64% of cases within 2 years following treatment [15].

In terms of comparison Tang *et al*., showed that CMPI had a higher rate of RLR and distant metastases than CINS [27].

In our series no patient presented a loco-regional recurrence. We therefore did not detect a significant difference between CMPI and CINS in terms of loco-regional recurrence.

The average duration of distant metastases for pure and mixed CIMIC cases was 53.0 and 43.3 months respectively in a study done by Gokce *et al*., [21]. The most common site of distant metastasis was the lung in 50% of cases in this same study.

According to several studies, CMPI is characterized by frequent invasion of the adjacent skin [2, 15, 26].

In our series, only one patient presented distant metastases during follow-up in the pulmonary site at an interval of 3 years. We did not identify a significant association between the 2 study groups.

Finally moving on to the CMPI survival rate which was inconsistent and a subject of debate between the different authors.

Kaya *et al*., [24] in their study demonstrated a survival rate of 81.4% over an average follow-up duration of 48.87 months.

A case-control study done by Vingiani indicated that CMPI had a similar survival outcome with CINS. However, the small size of the sample (49 CMPI versus 98 CINS) could compromise the effectiveness of these results.[28].

The study by Chen *et al*., [1] included 984 CMPI stage I-III cases with relatively adequate follow-up. This was a multivariate analysis bringing together all the risk factors: Height, histological grade, lymph node status and hormonal status. They concluded that CMPI had a better survival outcome than CINS.

According to Lewis. G *et al*., the survival rateewas variable in the bededeletion between 46% [5] and 87.5% [30].

Several prognostic factors influencing this survival have been studied in the literature. Numerous studies have proven that lymphovascular invasion is significantly correlated with loco-regional recurrence of CMPI [28], it is therefore not difficult to understand the results, given the high proportions of CMPI VEs. In our series we could not find a statistically significant correlation between the existence of EVs and OS.

Guo *et al*., [31] found that nodal status is an important predictor of overall survival rate. Some authors considered estrogen receptor negativity and high mitotic activity to have prognostic significance [15, 32, 33].

D. Lewis *et al*., showed through their studies that HR positivity was associated with a favorable prognosis and a long overall survival time. This was consistent with our study.

In attempting to identify prognostic factors in breast CMPI, Luna-More *et al*., [34] found that nuclear grade and extensive lymphatic invasion were important variables. Other factors, such as ER, RP, HER-2/neu protein overexpression, and p53 deletions have also been studied. It appears that the presence or absence of these markers in invasive micropapillary carcinoma generally mimics that of any breast cancer in terms of predicting patient prognosis [35, 26].

CONCLUSION

In conclusion, CMPI represents a particular variety of breast carcinomas. Through this study, we tried to dissect its different epidemiological, clinical, radiological and therapeutic characteristics which largely agreed with the literature.

The lack of perspective and the recent and reduced knowledge of this rare entity do not authorize, to date, a change in the therapeutic and monitoring protocol.

Conflicts of Interest: The authors declare no conflict of interest.

Author Contributions

All authors contributed to the conduct of this work. They also declare having read and approved the final version of the manuscript.

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