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Clinical Features and Outcome of Inflammatory Breast Cancer in Moroccan Population: Experience of Oncology Department of National Institute of Rabat

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Abstract- *Background:* Inflammatory breast cancer (IBC) is a clinical condition characterized by varied incidence, geographical distribution, and poor prognosis. We conducted this study to trace his epidemiological and immunihistochemical, evolution.

Methods: Case files were collected from the archives of the National Institute of Oncology. Inclusion criteria included:

– Aproven histological diagnosis of breast cancer
– Skin erythema over at least one third of breast
– Symptoms appearing over a period of under six months

Results: We collected 172 cases, incidence was 5%.Erythema in more than one third of the breast, orange peel skin and edema was present in all patients.126 patients had a localized disease ,46 patients were metastatic.

Keywords: *inflammatory breast cancer, neoadjuvant chemotherapy, pathological complete response, moroccan, hormonal receptor, her2neu.*

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64% of patients with localized disease showed axillary lymph node activity, and 9,.3% supraclavicular adenopathy . The most common histological type was invasive ductal carcinoma, 95.6%. In 42.4%(n=59) of the cases, hormonal receptors were negative. Human epidermal growth factor 2 (HER2) status was positive in 59 %(n=52) of the cases. In 88% of the cases (n=109), anthracyclines were administered. Anthracyclines and taxane was delivered to 15 patients (12%).

Among 124 patients with local disease, 77.4% (n=96) were operated on. pCR (pathological complete response) was 4,8% (n=6).

Median overall survival (OS) in non metastatic patients was 16.5 months, three and five year's OS were respectively 11 % and 3%.

Conclusions: Our study confirms the higher incidence of IBC in Moroccan population comparatively to American and European populations. Positivity of HER2 was higher. Treatment used was insufficient, with poor survival. We have started a prospective registry of IBC in our institute.

Keywords: inflammatory breast cancer, neoadjuvant chemotherapy, pathological complete response, moroccan, hormonal receptor, her2neu.

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I. Background

Inflammatory breast cancer (IBC) is an uncommon form of breast cancer which represents the most aggressive manifestation of breast cancer, with a very poor prognosis. It has a particular geographical distribution with a higher incidence in North Africa-about 5-7% of all breast cancer cases [1].

At the National Institute of Oncology in Rabat, the first recruitment center in Morocco, we realized a retrospective study aimed at evaluating the incidence of this rare type of breast cancer in the country, tracing its immunhistochemical profile, and evaluating patient treatment and survival.

II. Methods

This is a retrospective study covering the period of January 2005 to December 2008, performed at the National institute of Oncology of Rabat.

We conducted our study based on clinical, histological and therapeutic data collected from the files of patients with inflammatory breast cancer available in the archives of the institute. Incomplete files were excluded.

Inclusion criteria of our study were: histological evidence of breast cancer and onset of inflammatory signs in less than 6 months. Twelve hundred sixty cases met our inclusion criteria.

Inclusion criteria of primary inflammatory breast carcinoma (IBC) include: a proven histological diagnosis of breast cancer, skin erythema in over one third of the breast, symptoms appearing over a period of less than six months.

All patients underwent chest radiography, abdominal ultrasound, and bone scans. The data collected from the patient's medical file included: age, time of onset of symptoms, clinical diagnosis, nodal involvement, stage, treatment received (chemotherapy, surgery, radiotherapy) and date of death or last visit.

Pathological complete response (pCR) was evaluated by Chevalier classification, which studied the response in both breast and lymph nodes: Grade 1 and

2 correspond to obtaining a complete response; Grade 3 includes invasive carcinoma with tumor alterations; Grade 4 is defined by few alterations or absence of alterations of tumor cells.

a) Statistical methods

Data was analysed using SPSS 13 software. Overall survival and progression-free survival were estimated by the Kaplan-Meier method. A log-rank test was used to compare survival rates. The test was conducted at a 5% significance level. Descriptive statics with 95% confidence interval (CI) were calculated according to standard procedure.

III. Results

a) Patient characteristics

Between January 2005 and December 2008, out of the three thousand four hundred cases of cancer identified, one hundred seventy-two patients were identified as having inflammatory breast cancer; the incidence was 5%.

Patient age included in the study was 27 to 75 years (Figure 1), with a median of 46 years. The occurrence of inflammatory breast cancer was higher in patients between 40 and 49 years (n=68), 39, 5%. Non-menopausal women constituted 58% of the patients.

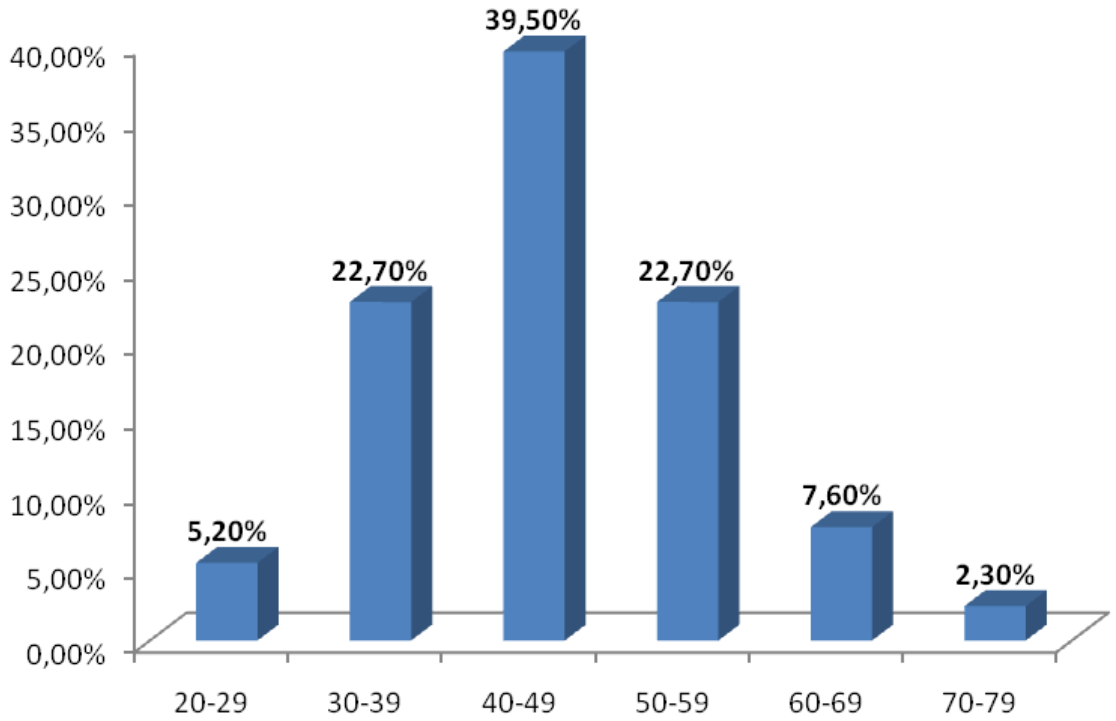

Figure 1 : Distribution of patients according to age

The time of the appearance of symptoms was less than six months in all patients, as defined in the inclusion criteria, to differentiate between a true inflammatory and locally advanced breast cancer. In half of the patients, the signs of inflammation appeared within three months.

b) Clinical features

Signs found in all patients upon clinical examination were: Erythema over more than one third of the breast, or orange peel skin, and edema. However, in 26.7% of the cases, no palpable mass was found.

Axillary lymphadenopathy was found in 64% (n=110), and the supraclavicular lymph node in 9.3% (n=16).

After staging, 27% (46) of the patients (n=46) had metastases at the onset. The metastasis site was: bone (n=32), liver (n=16), lung (n=17), and brain tissue (n=7). However, 39% (n=18) of the patients had multiple synchronous metastases (Table 1)

Table 1: The different metastasis site

Metastasis site	Number of patients
Bone	32 (69,5%)
Lung	17 (36,9%)
Liver	16 (34,7%)
Brain	7 (15,2%)
Multiple sites	18 (39%)

c) Histological and immunohistochemical features

The dominant histological type found was invasive ductal carcinoma (95.6%). Invasive lobular carcinoma was second, at only (3.4%), other histological types were found in 1% of cases.

94% of patients' tumors showed an aggressive profile, with grade SBR 2 and 3. Only 6 % of tumors were grade 1.

Hormonal receptor status couldn't be determined in 19%. The criterion of hormonal receptor negativity was ER and PR negative, the rate of negative receptors was 42.4% (n=59).

Human epidermal growth factor 2 (HER2) status was positive in 59% of cases, but research of HER2 status was done on only 51% of all patients (n=88) (Table 2)

Table 2 : Clinicopathological characteristics of patients

Median age	46 years
Histological type	
Infiltrating ductal carcinoma	95,6% (n=161)
Invasive lobular carcinoma	3,4% (n=9)
Other	1% (n=2)

SBR grade	
I	6% (10)
II	54% (92)
III	40% (68)
Hormone receptors	
Negative	42,4% (59)
Positive	57,6% (80)
HER2	
Negative	41% (36)
Positive	59% (52)

d) Treatment

Among 126 patients with no metastatic disease, 2 patients couldn't receive chemotherapy because of an ECOG performans staus higher than 2.

Anthracyclines were administered in 88% of cases (n=109). The most commonly used protocol was the AC60 regimen (Anthracycline:60mg/m^2, cyclophosphamide:600mg/m^2) followed by the FEC 100 (5Fu:500 mg/m^2, Epirubicine:100mg/m^2, Cyclophosphamide: 500 mg/m). An association of sequential anthracyclines and taxane was administered to only 15 patients (12%). Patients received an average of 4 neoadjuvant cycles, with a minimum of 3 cycles and a maximum of 9.

Among 124 patients with localized disease we obtained 77.4% (n=96) of clinical response, a Patey was realized in all these patients. Some patients were inoperable, mainly due to the lack of response to neoadjuvant chemotherapy or clinical progression.

After surgery, an evaluation was made to the histological response in the breast based on the CHEVALIER classification, 8,8% (n=11) of our patients had a pathological complete response (pCR) in the breast. A lymphnodes complete histological response was found in 15,3% (n=19) of cases. pCR in both breast and nodes was obtained in 4,8% of cases (n=6).

Treatment of metastatic patients consisted on palliative chemotherapy .Protocols were heterogeneous, mainly anthracyclines in 80,6% of cases,10,8% (n=5) of cases received auther regimens (FUN,CMF)

8,6%(n=4) patients did not receive chemotherapy due to performans status higher than 2.

e) Follow-up

Patients were followed up for five years. Patients who were not reviewed in the last consultation were subsequently contacted by telephone. Monitoring was organized over several visits: every three months for two years, every 6 months for a year, then once a year.

f) Survival

Median overall survival (OS) for patients with localized disease was 16,5 months. Three and five year OS were respectively 11% and 3% (Figure 2).

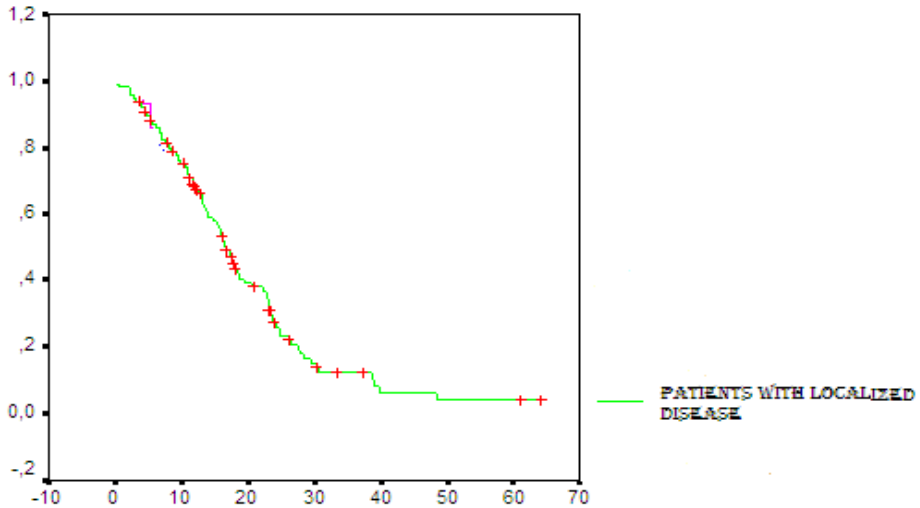

Figure 2 : OS in patients with localized disease

During the follow-up, the evolution has been characterized by local recurrence in seventeen cases (27,5% of all patients). Metastasis occurred in 48 cases. The site of metastasis was lung in fourteen cases; the bone in eleven cases, liver in eight cases; lymph node and brain in eight and four patients respectively.

Metastatic patient survival was poor, with a median overall survival of 11.6 months. OS at 2 and three years was 1.5% and 0% respectively (Figure 3).

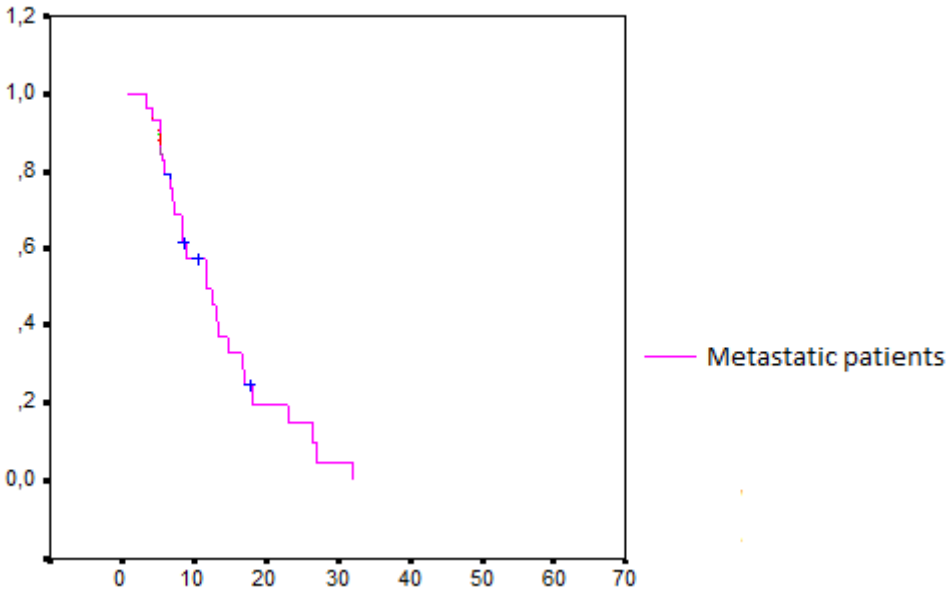

Figure 3 : OS in metastatic patients

Patient survival was influenced by the presence or not of metastases (p<0,0001) and hormonal status, patients with positive hormonal receptors had a better survival (p<0,002).

The difference in survival between patients with HER2 positive status and those with a negative HER2 was not statistically significant (p = 0.08), this is explained by the large number of patients (n=84) who have not benefited from the study of HER2 status.

IV. Discussion

Inflammatory breast cancer is now distinguished from other forms of locally advanced breast cancer. It is characterized by its clinical presentation and its severity. It accounts for about 1-7% of breast cancers with a frequency depending on the country (higher in the Maghreb countries including Tunisia). The current study represents a large retrospective review of 172 patients with a diagnosis of inflammatory breast cancer treated at our institute over four years (2005-2008). In our study, the incidence found was 5%. In the Tunisian study, Mourali, the incidence rises to 5.6% [2], which confirms the elevated frequency of this type of cancer in North African countries.. In the United States and Europe, IBC is particularly rare, its frequency not exceeding 3% in a wide study by the American SEER program (Surveillance Epidemiology and End Results), and 1% in Japan (Table 3) [3]

Table 3 : Incidence of IBC by country

OUR STUDY	5%
Japan	1%
USA(SEER)	1,9%
Spain	3%
ITALIE	3%
TUNIS	5,6%

Several medical teams have tried to identify risk factors related to this type of cancer; Tunisian studies have confirmed that the young age is a risk factor. Data from the SEER (Surveillance Epidemiology and end results program) show a higher incidence in the African-American race; this has been confirmed also by studying Chang-Shine (USA). Others factors are involved, such as the young age of first pregnancy, obesity. Mouse mammary tumor virus (MMTV) sequences have been reported to be present in some human breast cancers, recently, it has been shown that in addition to activation of cellular proto-oncogenes, MMTV can contribute to mammary tumorigenesis by direct transformation of normal human epithelial cells by expression of signaling proteins [4] [5].

Clinically, the diagnosis of inflammatory carcinoma is essentially based on an onset of

symptoms within six months: Erythema over at least one third of the breast, edema, and warm breast, with or without an underlying palpable mass. Histological evidence of the presence of cancer is imperative [6]. All our patients saw their symptoms appear in less than 6 months.

The particularity of these neoplastic entities results not only in its clinical presentation, but also in terms of its bio molecular profile. Inflammatory carcinoma histology shows no specificity compared to other forms of cancer .The largely predominant histological type in the entire study is invasive ductal carcinoma, representing between 87% and 95%, the same result was found in our study with 89.5% (n=154) of invasive ductal carcinoma. But we must remember that there is no histological type specific to inflammatory breast cancer [7] .The real hallmark is the presence of dermal lymphatic invasion by lymphatic emboli. These emboli are responsible for the characteristics and clinical symptoms (color, edema), as well as high metastatic potential of breast cancer [6]. Skin biopsy remains important for the demonstration of emboli but not essential for confirmation of the diagnosis [8]

The molecular alterations usually reported in IBC include: Low expression levels of the hormone receptor, Paradiso and al, Boussen and al. Studies show more frequent negative estrogen and progesterone status in patients with inflammatory carcinoma than others [1][9]. Negativity of receptors is associated with poor survival rate [10]. In our study, we find 42.4 % of negative receptors, however, 19% of our patients have not benefited from the research of RH status.

Human epidermal growth factor receptor 2(HER2) is a proto-oncogene located in the long arm of chromosome 17 (17q21) and encodes a trans membrane receptor, tyrosine kinase. Its appearance is generally amplified in breast cancer. Furthermore, IBC has a higher percentage, thus reflecting its aggressive potential. Paradiso and al have used the results of 49 biopsies taken in patients with inflammatory breast cancer, 42% of these samples tested positive for HER2neu [9].The Tunisian Ben Hamida study supports these findings, objectifying the rate of HER2 amplification of 33.3% versus 14.5% in non-inflammatory cancers [11]. Our results are consistent with those findings, with 59 % of HER2 positivity detected (Table 4).

Table 4 : HER2 expression in the different series

study	Rate of expression of HER2
Chaher [12]	20%
Paradiso [9]	49%
Ben hamida [11]	33,3%
Our study	59%

Other characteristics of IBC tumors include a high expression of human epidermal growth factor receptor (EGFR), thus promoting increased transcription of cellular DNA [12][13]. There is also an over expression of a proto-oncogene p53-with a high mutation rate [14] E-cadherin is also over expressed, this molecule promote intercellular adhesion tumor, and the formation of tumor emboli infiltrating the lymphatic dermis [15][16].

Van Golen have identified the lack of a specific molecule IBC: WISP3 or LIBC (lost in inflammatory breast cancer), data indicate that LIBC/WISP3 acts as a tumor suppressor gene in breast [17]. Comparison of gene expression between human IBC and non-IBC tumor samples revealed overexpression of RhoC, which gives to IBC an invasive phenotype with a high metastatic potential [18].

In the MD Anderson study, 178 patients with inflammatory carcinoma were treated with primary chemotherapy centered on doxorubicin; patients subsequently received local treatment with radiotherapy or mastectomy followed by adjuvant chemotherapy. Overall survival rate within 5 years was 40%, with a median overall survival of 37 months. Histological responses to chemotherapy were obtained in 71% of cases, with 12% of pathological complete responses. 88% of our patients received only anthracyclines (AC60, FEC100), we obtained 66% of histological responses [19].

Nevertheless, integration of taxanes into combination chemotherapy has shown efficacy in neoadjuvant treatment. In retrospective analysis of M.Cristofanilli and al, with 240 patients included in 6 studies between 1973 and 2000, the addition of paclitaxel to anthracycline (FAC) increased the pCR rate by 15% (25% for FAC and paclitaxel versus 10% for FAC alone), progression-free survival and overall survival rate [20].

The largest study of patients with IBC who received Trastuzumab was reported from NOAH (neoadjuvant Trastuzumab) phase 3 trials. it included 343 HER2 positive patients, and it evaluated the benefits of adding Trastuzumab to neoadjuvant chemotherapy. Amongst the76 patients with HER2-positive IBC, a significantly higher pathological complete response rate (54.8%) was noted in women who received standard doxorubicin, paclitaxel, and cyclophosphamide chemotherapy with Trastuzumab than in women who received standard therapy without Trastuzumab (19.3%) [21]. In our study, no patient received Trastuzumab because it was unavailable until 2009.

Clinical complete response in the breast is defined by the absence of inflammation and clinical mass, with or without clinical complete response at the nodes [22].

Data from collected works reported a poor correlation between complete clinical response and histology. In a recent study on a group of 89 patients preoperatively treated with anthracyclines, 15 (17%) had a complete clinical response with only 3

histopathological complete responses [23]. In our study, 77.4% of patients obtained clinical complete response, but complete histological response is noted in only 6 patients (4.8%). The study of Belembaogo and colleagues lead to similar gaps [24].

The study of Kuerer showed that pathological complete response obtained at the mammary gland or axillary lymph nodes is indicative of improved survival rate [25].

The prognosis of inflammatory breast cancer is unfavorable due to early metastatic spread and local recurrence. But a combination of chemotherapy, surgery, and radiotherapy has been a major breakthrough over the last three decades, As a result, survival rates have improved significantly, with 15-year survival rates of 20% to 30% reported [2][26] . In the Tunisian study of Boussen [1], the survival rate within 5 years was 8.52%, in our study it was 20%.

This is can be due to a suboptimal treatment neoadjuvant: only 12% of our patients received taxanes, and trastuzumab was not administered although 59% of patients were HER2 positive.

But it can also be due to the aggressive profile of inflammatory carcinoma in the Maghreb. SEER data support this hypothesis: a higher incidence of this type of cancer was observed in the African-American race [3]. Only an international multicenter observational study can answer to this probable difference in incidence and prognosis.

Two other features are added to the biological profile of inflammatory carcinoma: the angiogenesis and lymphogenesis. Mc Carthy and al. reported a significant increase in intratumoral microvessel density [27]. Indeed, Colpaert and al, showed intense angiogenesis by the percentage of high endothelial cells [16]. Based on this data BEVERLY sudy has evaluated efficacy and safety of neoadjuvant bevacizumab combined with trastuzumab and chemotherapy in patients with primary HER2-positive inflammatory breast cancer, 63,5% had a pathological complete response [28].

Recent data showed that the ALK gene is amplified in the IBC cell lines, in nine of the 12 patient tumors analyzed; However without detection of any activating mutations in the ALK gene, which are common in non–small-cell lung cancer [29].

V. Conclusion

Through our retrospective study, we have once again affirm that inflammatory breast cancer is a very aggressive tumor, with markers of poor prognosis, 59% of our patients expressing HER2, with a high rate of hormone receptor negativity whose mechanisms of action are still poorly understood, explaining his mediocre survival , 3% survival at 5 years.

A prospective study is underway the institute, to determine the contribution of targeted therapies in inflammatory carcinoma.

Abbreviations

IBC: inflammatory breast cancer

HER2: Human epidermal growth factor receptor 2

OS: overall survival

AC: adriamycine, cyclophosphamide

FEC: 5fluoro uracile, eprubicine, cyclophosphamide

FAC: 5fluoro uracile, adriamycine, cyclophosphamide

FUN: 5 fluoro uracile, navelbine

CMF: cyclophosphamide, metotrexate, 5 fluoruracile

SEER: Surveillance Epidemiology and End Results

pCR: pathological complete response

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

i.Ouziane: conceived of the study, participated in its design and coordination, contributed to the acquisition, analysis and interpretation of data and drafted the manuscript.

y.Bensouda: conceived of the study, participated in its design and coordination, contributed to the acquisition, analysis and interpretation of data and drafted the manuscript.

h.M'rabti: participated in the design and coordination of manuscript.

f.Elomrani: contributed to the acquisition and analysis of data.

n.Elismaili: conceived of the study, participated in its design and contributed to the acquisition of data.

S.Laanaz: contributed to the acquisition and analysis of data.

h. Elyacoubi: contributed to the acquisition and analysis of data.

N.Berrada: contributed to the acquisition and analysis of data.

S.Boutayeb: contributed to the interpretation of data.

h.Errihani: conceived of the study, participated in its design.

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