Biological features of inflammatory breast cancer in North Africa: burden and research priorities

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Practice points

- Data about inflammatory breast cancer in North Africa is lacking.
- Heterogeneous reports show differences between North African countries.
- Several actions with high impact can be initiated to improve outcome.
- Multicenter studies are needed.

We aimed to review all published literature reporting biological data about inflammatory breast cancer (IBC) in populations from North Africa. **Methods:** We reviewed all studies that evaluated biological features of IBC in six North African countries between 1990 and 2017. Among 118 screened studies, 13 were included, none about Mauritania/Libya. **Results:** Across the studies, hormonal receptors were positive in 46–69% of cases, reaching 83% in Algeria. HER2 was overexpressed in 25–39% of cases. Recombinant human C protein expression was the highest in Egyptian patients (87%) compared with other North African populations. Using mRNA expression recombinant human C protein was expressed in 83% of Tunisian patients. WISP3 gene expression showed positive immunohistochemistry staining in 17% and mRNA expression in 26.8% of IBC. **Conclusion:** Biological aspects of IBC across North Africa show important similarities and differences.

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Inflammatory breast cancer (IBC) is the most fatal form of breast cancer, responsible for a higher number of deaths compared with the non-IBC [1]. The epidemiology of IBC remains under investigation for its relative rarity; the incidence represents approximately 2–3% of breast cancers (BC) in the USA and 6–10% in North Africa [2,3]. There has been a considerable investigative effort on IBC in North Africa, where studies demonstrated more accurate epidemiological trends compared with historical reports of IBC (incidence of 5–7% with tumor-node-metastasis (TNM) staging vs 50% with PEV [poussée évolutive] classification) [3]. Several studies also reported clinical aspects and described the poor outcome [4]. Clinical definition on which the diagnosis of IBC relies entirely, is now well defined and used in clinical practice since the 6th edition of TNM classification in 2002 than in the additional refinements introduced by the international expert panel on IBC in 2010 [5]. Several studies reported different clinical aspects of IBC between North African patients and western patients in terms of risk factors, presentation and outcome [6,7]. Those differences were also reported within North African countries especially Morocco, Tunisia and Egypt. A study by Soliman *et al.* comparing IBC in those three countries showed that Egyptian IBC patients had the highest combined erythema, edema, peau d'orange and metastasis rate [8]. Those studies also reported differences in molecular features. Management of breast cancer is currently based on personalized medicine with an important role of tumor biology. Such data about IBC in North Africa are lacking. Most studies are single institution and/or single country. In our paper we reviewed the available published data on biological characteristics of IBC exclusively in six North African countries: Mauritania, Morocco, Algeria, Tunisia, Libya and Egypt. Such a study

Table 1. Studies reporting biological aspects of inflammatory breast cancer in North Africa.

Study	Year	Region	Number of patients	Study subject	Ref.
Lo <i>et al.</i>	2009	Egypt	46	RhoC expression and tumor emboli in IBC versus non-IBC	[10]
Lo <i>et al.</i>	2008	Egypt	48	RhoC GTPase IBC (Egypt) versus IBC (USA)	[11]
Soliman <i>et al.</i>	2012	Egypt Tunisia Morocco	48 24 42	RhoC GTPase and E-cadherine expression in IBC (Egypt) versus IBC (Tunisia) versus IBC (Morocco)	[8]
Ouziane	2011	Morocco	172	Clinico-pathological characteristics	[12]
Ismail <i>et al.</i>	2014	Morocco	72	Clinico-pathological characteristics	[13]
Chaher <i>et al.</i>	2012	Algeria	117	Molecular and epidemiological characteristics	[14]
Hamdi <i>et al.</i>	2016	Tunisia	20	Prognostic value of circulating miARNs	[15]
Le	2008	Tunisia	187	Prognostic value of dermal emboli in IBC (Tunisia) versus IBC (France)	[6]
Marrakchi	2010	Tunisia	41	WISP3 and RhoC expression between IBC and non-IBCuilk;hnb	[16]
Mejri <i>et al.</i>	2015	Tunisia	208	Epidemiological change in IBC	[9]
Labidi	2007	Tunisia	100	Therapeutic outcome	[4]
Charafe-Jauffret	2007	Tunisia	91	Expression of estrogen receptor, Ki67, E-cadherin, MUC1 and ERBB2 in IBC (Tunisia) versus IBC (France)	[7]
Ben Hamida <i>et al.</i>	2007	Tunisia	91	Distribution of molecular subtypes	[18]

IBC: Inflammatory breast cancer.

may provide some insights on the biological characteristics of the disease and would help improve understanding of its behavior.

Methods

We conducted a computerized Medline and Google scholar search using the limits 'French' and 'English' about published literature between January 1990 and June 2017, and using the Mesh terms: inflammatory breast cancer*, North Africa*, Mauritania*, Morocco*, Algeria*, Tunisia*, Libya* and Egypt*. References were hand searched for other references. Our inclusion criteria included retrospective studies, case-control studies, cohort studies and clinical trials. In addition, the bibliographies of recent reviews and the authors' personal holdings were checked to ensure that all relevant articles were consulted. A total of 118 studies were identified. The titles and abstracts of all retrieved articles were screened for the relevance. Articles in French were screened and handled for data extraction by the authors who are all fluent in French. Our exclusion criteria were: article about breast cancer not providing specific results about IBC group (46 studies), articles addressing mixed populations with patients from other countries without available data specific to our target population (23 studies) and articles not reporting any data on tumor biology, pathology and molecular pathology (36 studies). Biological data were defined as data including at least pathology features of the tumors such as histological subtype, grade, immunohistochemistry (IHC). Data were extracted using a prepiloted data extraction form and entered into a computerized database conducted specially for the study.

Statistical analysis

For each study, the effect size (standardized mean difference between treatment and control groups) was calculated and adjusted for sample size. Data were combined in a comprehensive analysis, both by calculating weighted average effect sizes and by looking at the percentage of studies with a positive or negative direction of effect.

Results

We identified 13 studies reporting data about tumor biology of IBC. Descriptions of those studies: author, year of publication, study population, sample size, and purpose of the study, were presented in [Table 1](#). Across all studies, the median age of IBC was 45 years old, ranging from 42 to 59 years old. Means and standard deviations of age were not reported in major studies.

Pathology aspects

Grade of IBC was reported in all 13 studies. Grade I was rarely observed in IBC cases in almost all studies, with a rate of 4% of cases. Across studies, IBC was grade II in 5–83%, and grade III in 17–90%. IBC was grade II in

Table 2. Distribution of pathological and immunohistochemistry aspects of inflammatory breast cancer among North African studies.

Study (patients)	Age	Grade			ER/PR		Her2 (%)	
		I	II	III	Positive	Negative	Positive	Negative
An Chi (46)	46.9	0	83	17	61	39	–	–
An Ch (48)	46.9	0	83	17	58.1	41.9	–	–
Soliman	43	0	83	17	61.1	38.9	–	–
Egypt (48)	46	8.3	12.5	79.1	54.6	45.4		
Tunisia (24)	54	0	50	50	46.7	53.3		
Morocco (42)								
Ouziane (172)	46	6	54	40	57.5 ER = 49 PR = 71	42.5 ER = 51 PR = 29	59	41
Ismail (72)	47	4	36	23 [†]	69	5.6 [‡]	25.5	74.4
Chaher (117)	59% <50 years	0	63	37	83	17	19.8	80.2
Hamdi (20)	49	0	45	55	ER = 15 PR = 20	ER = 85 PR = 80	65	35
Le (187)			55	45	63.1 ER = 50 PR = 47	34.9 ER = 50 PR = 53	–	–
Marrakchi (127)	45	0	36.5	63.5	ER = 41 PR = 27	ER = 58.5 PR = 73	–	–
Mejri (208)	45	10		(90)	48	52	31	69
Labidi (100)	43.5	4	39	37 [§]	ER = 17 PR = 12	ER = 40 PR = 27 [¶]	–	–
Charafe-Jauffert (91)	42	2.8	67	30	ER = 49	ER = 61	39.1 score 2–3	61.1
Ben Hamida (91)	43	3.3	66	30.7	ER = 46.1 PR = 47.1	ER = 53.8 PR = 52.8	33.6 score 2–3	66.7

[†] 37% unknown
[‡] 25.4% unknown
[§] 20% unknown
[¶] Unknown status
[#] ER: Estrogen receptors; Her2: Human epidermal growth factor receptor 2; PR: Progesterone receptors.

83% of Egyptian IBC patients [8,10,11], 36–54% of Moroccan IBC patients [12,13], 63% of Algerian patients [14] and 36–64% in Tunisian IBC patients [9,15–19]. In the largest series, by our team, 90% of the IBC cases were grade III [9], and in another IBC series about Tunisian patients by Soliman *et al.* [8] grade III was seen in 71% of cases. IHC aspects were reported in all studies with regard to hormonal receptors (HR) (estrogen [ER] and progesterone receptors) and only 7/13 studies reported HER2 status. HR receptors were positive in 15–83% of IBC cases. In the Algerian series HR were positive in 83% of IBC cases [14]. HER2 was overexpressed in 25–39% of cases, in one Moroccan study of 172 patients with IBC, HER2 was overexpressed in 59% [12]. The unique series where IHC subgroups of IBC were reported is the Algerian series [14]. The majority of IBC tumors were luminal A in 62.4% of cases, followed by basal in 17.7%, triple negative in 17.2%, Luminal B in 9.9% and HER2+ in 9.9%. Pathological characteristics of IBC through North African studies was described in Table 2.

Molecular aspects

Two genes were studied in IBC studies: loss of Human WNT1-inducible-signaling pathway protein 3 (WISP3) and overexpression of recombinant human C protein (RhoC) guanosine triphosphatase (GTPase). RhoC GTPase is a member of the Ras superfamily of small GTPases, microarray analysis has shown that expression of RhoC is progressively increased as tumors become more aggressively metastatic and that RhoC expression promotes metastasis. The second gene that is WISP3, several mutations in the WISP3 coding sequence are associated with tissue dysplasia and hypertrophy, WISP3 has also growth and angiogenesis inhibitory functions. Those two genes were reported to be consistently and concordantly altered in human IBC.

RhoC expression was evaluated in three studies and WISP3 in one. All studies used IHC staining for RhoC evaluation, with the Tunisian study evaluating both RhoC and WISP3 genes using both IHC and mRNA expression using reverse transcriptase analysis [8–16]. RhoC expression was the highest in Egyptian patients 87%, in Tunisian

Table 3. Recombinant human C protein expression evaluation among North African studies.

Study	RhoC expression (IHC)	miARN expression RhoC (RT-PCR)	Ref.
Lo <i>et al.</i>	Low 13% High 87%	–	[10,11]
Soliman <i>et al.</i>	Low 13%, high 87% Low 50%, high 50% Low 61.9%, high 38.1%	–	[8]
Marrakchi <i>et al.</i>	Negative 31.8% Positive 68.2%	Negative 17% Positive 83%	[16]

IHC: Immunohistochemistry.

patients it was over expressed in 50–68% and in Moroccan patients in 38.1%. Using mRNA expression RhoC was expressed in 83% of Tunisian patients. The second gene WISP3 was studied in one study about Tunisian patients [16] showing a positive IHC staining in 17% and mRNA expression in 26.8% of IBC. Data about RhoC results are summarized in [Table 3](#).

Discussion

The present analysis reported a review of pathological and molecular data yet published about IBC in North African countries. It showed heterogeneous aspects across North African IBC patients with several similarities and differences. It also showed lacking representative data about biological aspects of IBC in the region. Molecular and pathological differences in IBC have been noted between Arab and European or USA populations, which could be linked to the aggressive clinical behavior of IBC in Arab women [17–20]. However, despite the fact that North African populations share common demographic features, including a large family size, high rates of consanguinity and rapid population growth [21], data about BC behavior and especially IBC behavior is rare. In lack of a national cancer registry or a large retrospective study, there are few data about breast cancer in Libya and Mauritania. In a study by Boder *et al.* including patients with breast cancer in Libya followed over the course of 5 years, the incidence was approximately 18.89 new cases per 100,000 Libyan females with a median age of 44 years. According to the TNM classification, 11.1% were T4N0M0 or TxN3M0 without any specific results about T4d stage [22]. In the Mauritanian series no data were reported about IBC [23].

Age was the most stable reported aspect. Age at diagnosis of BC in general and of IBC in particular in North Africa was reported to be 10 years younger than western populations in many studies [20], in fact, the age of breast cancer was reported to be around 50 years in North Africa and 62 years in western populations [3]. Such a result can be explained by the young population pyramid [2].

We found a large variation of IHC subgroups of IBC with regard to HR and HER2 expression across North African population. In 2008, a world IBC consortium reported the largest series of 389 IBC samples collected from France, Belgium and USA that analyzed with a standardized platform. It showed that 75% of IBC belonged to the aggressive subtypes (basal like, HER2, claudin-low and Luminal B), Luminal A subgroup accounted for 19% of cases [24]. In the Algerian series, 62% of IBC tumors were Luminal A according to IHC completely different from European/US results. As has been previously published, in these countries the rate of ER+ disease is lower than non-IBC, and the reported rates of HER2 are higher than non-IBC.

It is not very accurate to identify luminal A subtypes from IHC; when IHC is used these are subtype surrogates, and it is critical to identify exactly which markers were used to classify as luminal A-like. Given the low IHC expression of ER noted in many studies, the likelihood of finding luminal A subtypes if it were examined in all of these studies is relatively low. Such results should be taken with caution, certified labs should be encouraged to better characterize breast cancer subtypes more accurately. Such IBC consortium dedicated to patients from North Africa is urgently needed. Multicenter studies within each country and in collaboration with the other countries are mandatory. In order to target limited-resource communities, North African countries need to focus research and interventions on areas that will lead to the maximum impact. IBC screening seems not to be a relevant area of action, since IBC occurs in young women for which mammograms are not accurate and have a clinical history less than 6 months, which can be mis-detected by standard screening programs. North African countries should improve the infrastructure for diagnosing and caring for BC patients. Such facilities are relatively well established in Morocco, Algeria, Tunisia and Egypt with presence of cancer centers; however, such infrastructure is needed in Libya and Mauritania. Filling the lack of HER2 information is a major opportunity to improve outcomes in

Northern Africa, as the response to anti HER2 drugs is high. Also, focusing on biology of IBC tumors seems to be a relevant area. Identifying prognostic factors and predictive factors would lead to a better use of personalized medicine. Outcome data would provide a more comprehensive picture of the disease in these regions, however, we were unable to find these data in the respective papers and therefore were unable to make conclusions on outcome results.

Future perspective

There is an urgent need for identification of molecular signature and pathways specific to IBC patients in order to promote drug development for this particular aggressive subgroup of BC. IBC patients should be included in clinical trials with new targeted therapies. Research in the region is lacking, and most advances in the understanding and management of this disease have been based on research conducted in the other northern populations that is not necessarily reproducible in North African patients. Difficulties in conducting such studies were reported by Soliman *et al.*, taking their experience in studying IBC in North African as an example [25]. They elaborated with a checklist, based on logistic, methodology and quality control factors, which summarizes important issues for conducting such studies and may help local researchers overcome obstacles.

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Ethical statement

This work was approved by the local ethical committee.

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