Section: Pathology

Original Research Article

EXPRESSION OF CD163 IN TUMOR ASSOCIATED MACROPHAGES IN TUMOR MICROENVIRONMENT OF CARCINOMA BREAST AND CORRELATION WITH HORMONAL STATUS

D. Gowri Manohari[1], R. Hemapriya[2], V. Martina[3]

[1]*Assistant Professor, Department of Pathology, Madras Medical College, India.*
[2]*Assistant Professor, Department of Pathology, Madras Medical College, India.*
[3]*Associate Professor, Department of Pathology, Stanley Medical College, India.*

Received *: 09/01/2026*
Received in revised form *: 20/02/2026*
Accepted *: 07/03/2026*

Corresponding Author:
Dr. D. Gowri Manohari
Assistant Professor, Department of Pathology, Madras Medical College, India.
Email: dr.gowriprasanna@gmail.Com

DOI: 10.70034/ijmedph.2026.1.587

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 3428-3435

ABSTRACT

Background: Breast carcinoma is the most common malignant tumor and the most common cause of carcinoma death in women with more than 1.7 million cases occurring worldwide annually. Clinical and pathological disease staging remains an important prognostic factors, many other prognostic markers are extensively under research . Many studies focus on association of disease with Tumor associated macrophages which forms one of the major component in the Tumor microenvironment .

Materials and Methods: This is a retrospective and prospective study conducted in the institute of pathology, Madras Medical College , Rajiv Gandhi Government General Hospital for a period of two years from from July 2017 to July 2019 with prior approval from Institution Ethics committee with IEC reg no ECR /270/Inst./TN/2013. Modified radical mastectomy specimens with appropriate clinical details were collected. Corresponding HPE slides are prepared from formalin fixed paraffin embedded tissue .The blocks are also subjected to ER, PR ,HER 2 NEU , KI 67 and CD 163 immunohistochemical markers . CD 163 is a macrophage marker which shows membranous positivity in macrophages. The expression of above markers were studied and correlated with age , sex , grade, histological Variant and hormone receptor positivity.

Results: Among 100 cases, 25cases(25%) show low macrophage infiltration, 49 cases(49%) show moderate infiltration and 26 cases(26%) show high infiltration.88% of IDC-NST and metaplastic carcinoma show high TAM infiltration. 3 cases of papillary carcinoma show moderate TAM infiltration . 20% of the cases (20/100) are triple negative. Of which 56% show high TAM infiltration and only 85 show moderate TAM infiltration.TAM infiltration correlated with triple negative breast carcinomas.

Conclusion: CD163 expression in the Tumor microenvironment of breast carcinomas are associated with higher grade , triple negative status in hormonal receptors expression adverse prognosis and early recurrence and metastasis.

Keywords: TAM - Tumor associated macrophage, CD-163, microenvironment, ER- Estrogen Receptor, PR- Progesterone Receptor, HER2 NEU.

INTRODUCTION

Breast Carcinoma is the most commonly diagnosed cancer in women (24.2%) , about one in four of all new cancer diagnosed in women worldwide are breast cancer. It is also the leading cause of cancer death in women (15%).[1] While significant improvements have been recorded in more developing countries, advances have been dramatic owing to effects of mammography.[2] In India the incidence of breast cancer is 25.8 per 100000 women and mortality is 1.7 per 1000000 women. Studies

suggest that the commonest age group affected is 41-50.

Tumorigenesis is a dynamic and complex process and has three phases tumor initiation, progression and metastases. The physiological state of tumor microenvironment is connected closely to evolution of tumor. The vital components of the TME are fibroblasts and myofibroblasts, adipocytes, immune and inflammatory cells, blood and lymphatic vascular channels, neuroendocrine cells and ECM. The role of immune response during breast cancer is incongruous and dynamic. Host immunity provides immunosurveillance by destroying the tumor cells.[3,4] which is best illustrated by the clinical association between the prognosis and the density, activity and composition of tumor immune infiltrate at diagnosis. Macrophages are the most prevalent immune cells in mammary tumors and exert a profound influence over the immunologic states of neoplastic tissue. The presence of tumor infiltrating lymphocytes and specific CD8+ cytotoxic T cells have been associated with successful response to chemotherapy and reduction in relative risk of death in breast cancer patients.[5,6] Although many immunosuppressive cell types have been identified such as regulatory T cells, myeloid-derived suppressor cells (MDSC), tumor associated macrophages (TAM) comprise the most abundant cells in breast tumor microenvironment. TAM exibit a unique and robust influence upon disease.[7] Macrophage infiltration in human mammary tumors is associated strongly with high grade, decreased survival, reduced relapse free survival and thus serves as a independent prognostic indicator of breast cancer.[8]

TAMs in Tumor Microenvironment:

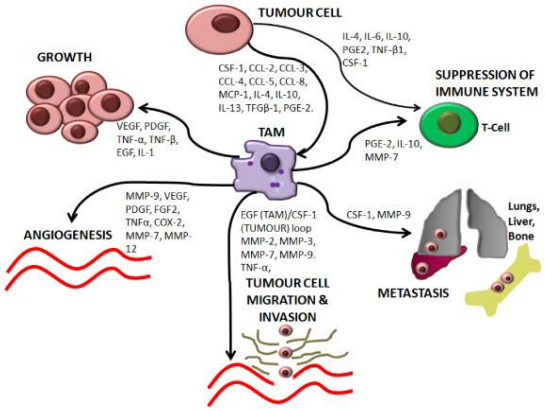

Figure 1: The role of TAM in tumor microenvironment

Once monocytes in the peripheral blood are recruited to the tumor, the tumor microenvironment promotes their differentiation into TAMs rapidly. The type 2 cytokine IL-4 secreted from Th-2 polarised CD4+ cells, IL-10 derived from regulatory T cells and immunoglobulin from B cells,[9] regulate macrophage polarisation to the promoter phenotype . Homeostatic imbalance: Hypoxia seems to promote malignant conversion and metastasis , which is mediated primarily through hypoxia –inducible factor HIF-1 alpha and HIF-2 alpha .the presence of high-mobility group box 1 protein (HMGB1) , extracellular ATP and other intracellular molecules is detected by Toll-like receptors(TLRs) present on the surface of the macrophages.[10] Tumor derived extracellular matrix components , including biglycan and hyaluronan are potentially important factors in directing TAM polarisation via TLR2 and TLR4.[11] These ECM components do not bind to TLRs in non-inflamed tissues but become TLR ligands following protease cleavage or interaction with reactive oxygen species, thereby forming putative sensory pathways for inflammation and tissue disruption.

TAMS PROMOTE CANCER PROGRESSION:

TAMs play crucial role in tumor progression, including cancer initiation and promotion, immune suppression , metastasis ,establishing a premalignant niche and angiogenesis.

Cancer initiation and promotion: TAMs connect inflammation and cancer. In 2009, cancer related inflammation was defined as a hallmark of cancer. Recent studies suggest that an inflammatory microenvironment promotes genetic instability within developing tumor epithelial cells and infiltrating or resident immune cells such as macrophages in inflammatory microenvironment . Kupffer cells can provide essential mitogens for the promotion of hepatocellular carcinoma through a nuclear factor kappaB(NK-kB) dependent signalling mechanism, because its ablation reduced tumor burden.[12]

Immune suppression: TAMs are the major immunoregulatory cells in tumors, and they participate in inhibiting cytotoxic T lymphocyte(CTL) responses in tumor microenvironment. IL-10 produced by TAMs induce the coexpression of PDL-1 in monocytes which also inhibit CTL responses.[13] In addition TAM derived PGE2 and and CCL17, CCL18 are chemotactic factors that results in the suppression of T cells in the tumor microenvironment.

METASTASIS AND PREMALIGNANT NICHE

The comprehensively described mechanism in which TAMs promote metastasis and establishment of premalignant niche.

TAMs can produce proteases, including matrix metallopeptidase (MMP) 2, MMP 7 and MMP9, cathepsin B , and cleaves the ECM and provide a conduit for malignant cells.[14] Several research suggests that TAM play a crucial role in the regulation of EMT in cancers. They play an important role in initiation and progression of EMT.[15]

TAMs play an important role in forming premetastatic niches in organs where they tumor will eventually metastasise. TNF alpha , VEGF and TGF beta are derived from TAMs and transported through the bloodstream to destination organs , where they induce TAMs to produce S100A8 and serum amyloid A3. Both can recruit macrophages and tumor cells to these organs and promote the formation of metastatic foci.[16]

ANGIOGENESIS

Studies have shown that the levels of TAMs are closely associated with the number of vessels in tumoral tissue. Hypoxia is a major factor for tumoral angiogenesis. Macrophages that accumulate in the hypoxic and necrotic areas express HIF-1alpha, which regulates the transcription of many genes such as VEGF, TNF alpha, IL-1 B and PDGF. These molecules are involved in angiogenesis, indicating that TAMs promote the formation of blood vessels intratumorally and provide nutrition for tumor growth.[17]

LOSS OF TUMORICIDAL FUNCTION BY MACROPHAGES IN TUMORS

Macrophages constitutes the major population of inflammatory cells and it is skewed by several factors in it and thus contributes significantly to the immunologic state of mammary tumors. Examined collectively TAMs undergo a marked shift in transcription factor expression, down regulating proinflammatory factors NF-KB, STAT 1whereas upregulating IRF4, STAT6, MYC, factors involved in tissue repair and remodelling.[18] The TME skews macrophage polarisation as well from the immunogenic cytokine production to trophic producing one . These macrophages also undergo a profound reduction of MHC class II expression inhibiting subsequent antigen presentation and adaptive immune response. Owing to their abundance in TME, the loss of tumoricidal function by macrophages represents a crucial breach in immunosurveillance thereby promoting development and progression of breast cancer.

THERAPEUTIC TARGETING OF TAMS:

With the knowledge about the role of TAMs in recurrence and metastases, current interventions has focussed on three strategies.

1. Blocking macrophage precursor recruitment, - targeting the prominent CSF1-CSF1R and CCL2-CCR2 signaling axis results in decreased monocyte mobilisation from the bone marrow. This eventually reduces precursor infiltration and macrophage differentiation within mammary tumors and pre-metatstatic sites.[19,20]
2. Depletion of TAMs and their progenitors – administration of immunotoxin-conjugated monoclonal antibodies targeting antigens expressed by TAMs ,such as scavenger receptor A ,CD52 and folate receptors beta was found to reduce TAM prevalence in ovarian and pancreatic cancer.[21] .Bisphosphanate compounds including Zoledronic acid are taken up by highly phagocytic cells like macrophages inhibiting their proliferation, migration and induces apoptosis . administration serially in a mouse model of spontaneous breast cancer have shown reduced neovascularisation, decreased TAM density and increased survival.[22] Treatment effects of Zoledranic acid were also associated with a shift of repolarisation of TAMs to a tumoricidal phenotype which is explained via inhibiting VEGF.[23]
3. Reprogramming macrophage within tumors.- macrophages within the early malignant tissue are tumoricidal , prolonged exposure to the TME endows macrophages with tumorigenic properties . when tumorigenic properties are therapeutically exploited antitumor properties of macrophage can be restored. Administration of toll-like receptor agonists including Imiquimod results in nuclear translocation of NF-KB in monocytes and macrophages with subsequent production of proinflammatory IFN A, TNF A, IL-6,IL-8 and IL12. Studies show delivery of TLR agonist may reprogram TAMs by restoring their ability to destroy breast cells. Studies show in a mouse model with a poorly immunogenic skin metastasis of breast tumor, a combination of Imiquimod and radiotherapy resulted in complete regression of metastatic skin lesion and when administered after cyclophosphamide to eliminate regulatory T cells, Imiquimod and radiotherapy completely ablated primary tumor.[24]

Aims and objectives:

To correlate ER,PR,HER2 neu status with expression of Tumor associated macrophages.

MATERIALS AND METHODS

Study Design and Setting

The present study “Expression of CD163 In Tumor Associated Macrophages In The Microenvironment Of Breast Carcinomas With Special Reference To Cancer Dormancy” was conducted in Institute of Pathology, Madras Medical college/ Rajiv Gandhi Government General Hospital from July 2017 to July 2019.

During the study period there were 1138 resected breast specimens received. Out of which 222 were non-neoplastic lesions, 512 were benign and 404 were malignant tumors.

Inclusion Criteria:

- Cases diagnosed as breast carcinoma in modified radical mastectomy specimens.

Exclusion Criteria

- Benign tumors
- Benign and malignant phyllodes
- Non neoplastic lesions of breast and
- Small biopsies.

Method of Data Collection:

Of the total cases reported during this study period, 92 cases from Invasive ductal carcinoma NOS and 8 cases from special types such as mucinous, metaplastic and papillary carcinomas were randomly selected . The detailed history of the cases regarding age, sex, side of the breast , type of procedure , details of gross characteristics such as tumor size, nodal status, lymphovascular and perineural invasion , ER ,PR and HER2 NEU expression was studied. Their representative formalin fixed paraffin embedded tissue samples were subjected for analysis of tumor associated macrophages with Haematoxylin and

Eosin stained slides and with CD163 expression by Immunohistochemistry.

IIMUNOHISTOCHEMICAL EVALUATION:

Immunohistochemical analysis of CD 163 were done in paraffin embedded tissue samples using supersensitive polymer HRP system based on non-biotin polymeric technology.

Antigen	Vendor	Species(clone)	Staining pattern	Positive control
CD163	Path insitu	Rabbit monoclonal	Cytoplasm	Normal splenic parenchyma

INTERPRETATION AND SCORING SYSTEM: ER AND PR

Hormone receptors like Estrogen and Progestrone receptor, when expressed show a nuclear positivity. The number of cells expressing and their intensity of staining as two values and a composite score based on percentage plus intensity of more than 2 is considered to be positive.

HER 2 NEU

HER 2 neu expression is demonstrated in tumor cells as cytoplasmic expression is graded as 1+,2+ and 3+.

EVALUATION OF TUMOR ASSOCIATED MACROPHAGES:

Tumor associated macrophages has been evaluated with CD163 expression by Immunohistochemistry. CD 163 expression is characterised by granular cytoplasmic or cytoplasmic and membranous staining patterns. Only the cells with monocytoid /macrophage like morphology were counted within the tumor stroma. The expression of CD163 was determined by counting the number of positive macrophages. We estimated the CD163 stained macrophages in five different fields in high power and an average was taken. We analysed the correlations between number of macrophages and the clinicopathological parameters and hormonal receptor status.

Statistical Analysis

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the association of significance in categorical data the Chi-Square test was used. In the above statistical tool the probability value .05 was considered as significant level.

CD 163 Expression was statistically analysed and categorised into

- Low macrophage infiltration (0-25%)
- Moderate macrophage infiltration (25-75%)
- High macrophage infiltration5 (75-100%)

RESULTS

Among the 100 study cases, all were diagnosed malignant following modified radical mastectomy and all were evaluated for ER, PR and HER2NEU expression

Regarding the histological types of breast carcinoma in present study there were 92 cases (93) % of Invasive Ductal Carcinoma –No Special Type, 2 cases (2%) each of mucinous carcinoma, papillary carcinoma and metaplastic carcinoma and one case(1%) presented as IDC with mucinous differentiation .

In present study the breast carcinomas were graded according to Modified Bloom Richardson scoring system inti Grade I,II and III. Amon the 100 cases grade II tumors constituted the most about and were grade III tumors.

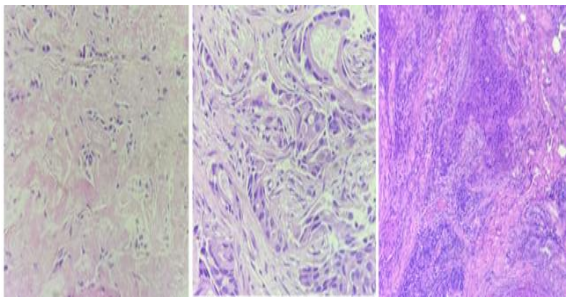

Figure 2:A) Invasive Breast Carcinoma -Grade I B) Grade Ii C) Grade III

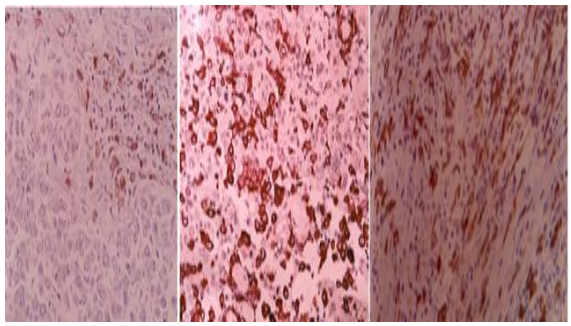

Figure 3: A: Low Tam Infiltration B: Moderate Tam Infiltration C: High Tam Infiltaration

Hormonal receptor status was evaluated in all the 100 study cases. Among the 100 cases, most of the cases were her2 neu + comprising about 39%, followed by triple negative tumors which were 20%, triple positive tumours were 19% ER+/PR+/H2N – were 13% and ER positive tumors 9%.

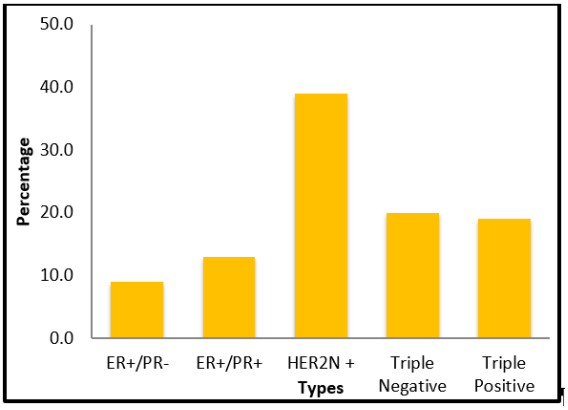

Figure 4: Distribution Based On Hormonal Receptor Status

Tumor associated macrophage expression is evaluated by Immunohistochemistry using CD163 marker. Macrophage infiltration was evaluated by counting the number of macrophages that has taken positive cytoplasmic or membranous staining. individual macrophages are counted in randomised high power fields and an average was taken, the macrophage infiltration was categorised into low, moderate and high by statistical analysis.

Among 100 cases, 25cases (25%) show low macrophage infiltration, 49 cases (49%) show moderate infiltration and 26 cases (26%) show high infiltration.

Table 1: Distribution of TAMs in breast carcinoma

TAMs	Frequency	Percentage
Low	25	25.0
Moderate	49	49.0
High	26	26.0
Total	100	100.0

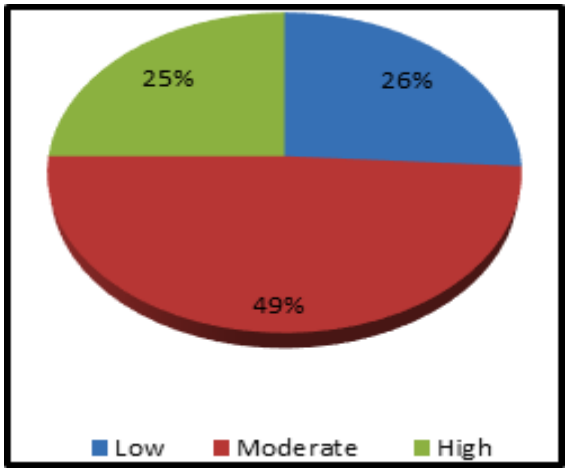

Figure 5: Distribution of TAMs in breast carcinoma

Among the 100 cases ,88% of IDC-NST and metaplastic carcinoma show high TAM infiltration. 3 cases of papillary carcinoma show moderate TAM infiltration. P value is not significant because TAM density is independent of histological subtypes.

Table 2: Correlation of Hormonal Status with TAMs

			TAM			Total	☐ 2 - value	P-value
			Mild	Moderate	Severe			
HORMONAL RECEPTOR STATUS	ER+/PR-	Count	4	4	1	9	40.933	0.0005 **
		%	15.4%	8.2%	4.0%	9.0%		
	ER+/PR+	Count	6	4	3	13		
		%	23.1%	8.2%	12.0%	13.0%		
	HER2N +	Count	5	28	6	39		
		%	19.2%	57.1%	24.0%	39.0%		
	TRIPLE NEGATIVE	Count	2	4	14	20		
		%	7.7%	8.2%	56.0%	20.0%		
		Count	9	9	1	19		

	TRIPLE POSITIVE	%	34.6%	18.4%	4.0%	19.0%		
Total		Count	26	49	25	100		
		%	100.0%	100.0%	100.0%	100.0%		
** Highly Significant at P < 0.01 level								

Among 100 cases, 39%(39/100) show HER2NEU positivity of which 57.1% show high TAM infiltration, 24% show high TAM infiltration and 19.2% show low TAM infiltration.

Among 100 cases, 20%(20/100) are triple negative. Of which 56% show high TAM infiltration and only 85 show moderate TAM infiltration.

Among the study cases19%(19/100) are triple positive tumors, in which 34.6% show low TAM infiltration and 18% show moderate TAM infiltration.

In present study 13%(13/100) are HER2NEU negative tumors with ER/PR positivity, of which 23% show low TAM infiltration and 12% show high TAM infiltration.

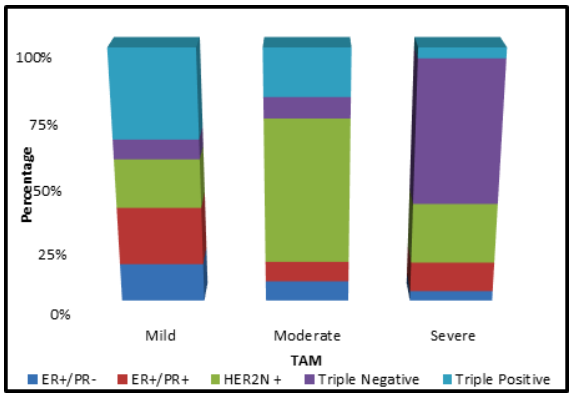

Figure 6: Correlation of TAM with Hormonal Status

DISCUSSION

Carcinoma breast is a heterogenous malignancy both clinically and pathologically. Mortality of breast cancer can be reduced by early detection, appropriate management and targeted therapies. There are many prognostic markers for breast carcinoma such as size, grade, nodal status, ER, PR, HER2 NEU status, and many prognostic factors in the tumor microenvironment like tumor infiltrating lymphocytes, tumor associated macrophages etc. TAMs play an important role in angiogenesis, invasion and metastasis. TAM impacts the prognosis of breast carcinoma. Tumor associated macrophages which are under extensive research and many targeted therapies against TAMs in carcinoma breast are under trial.

In the present study, TAMs in the breast tumor stroma was assessed by immunohistochemistry with the use of CD163 antibody and counted microscopically in five field and an average was taken. TAM density was categorised as low, moderate and high infiltration in the tumor stroma. An attempt was made to correlate the TAMs with clinicopathological features.

In present study among 100 study cases, 25%(25/100) show low TAM infiltration, 49%(49/100) show moderate infiltration and 26%(26/100) show high TAM infiltration. An attempt was made to correlate the TAMs with clinicopathological features.

DISTRIBUTION BASED ON HISTOLOGICAL TYPES

Among the histological subtypes, Invasive ductal carcinoma –NST type comprised the most common with 92% of cases, 1% was IDC with mucinous differentiation, 2% of mucinous carcinoma, 3% of papillary carcinoma and 2% of metaplastic carcinoma. William et al showed that IDC-NST was 91%, mucinous carcinoma 3%, papillary carcinoma 0.8% and medullary carcinoma 1.15.[25]

Table 3: Comparison of Histological Subtyping of the Tumors

Histological subtypes	William et al	Present study
IDC-NST	91%	92%
IDC with mucinous differentiation	-	1%
Mucinous carcinoma	3.3%	2%
Papillary carcinoma	-0.8%	2%
Metaplastic carcinoma	-	1%
Medullary carcinoma	1.3%	-

HORMONAL STATUS OF BREAST CARCINOMA:

In our study population 39% had HER2 NEU positive tumors, 22% had HER2 neu negative tumors, triple negative were20% and triple positive were 19%. Onitilio et al show68.9% cases are HER 2 neu negative followed by triple negative tumors comprising 13.4% and triple positive tumors 10.2

Table 4: Comparison of Hormonal Status

HORMONAL STATUS	Onitilio et al	PRESENT STUDY
ER/PR + H2N -	68.9%	22%
ER/PR- H2N +	7.5%	39%
TRIPLE POSITIVE	10.2%	19%
TRIPLE NEGATIVE	13.4%	20%

In our study, most of the large tumors are HER2 NEU positive, small sized tumors are HER2NEU negative, Onitilio et al show larger tumors are HER2NEU positive while smaller tumors are triple negative.

In our study most of the grade I tumors had Her2NEU negative status, among grade II tumors most of them are HER2 NEU positive, in grade III tumors , both triple negative and HER2NEU positive tumors are common .

Among nodal status, 64% of the triple negative tumors show no metastatic nodes, whereas 1-3 nodal positivity is seen in 45% of HER2 NEU negative tumors, 17% of triple negative tumors show 4-9 metastatic nodes and 13% of HER2 NEU positive tumors show more than 9 metastatic nodes. Onitilio et al show 63.5% of triple negative tumors show negative for metastatic nodes.

CORRELATION OF TAM DENSITY WITH HORMONAL STATUS

IN OUR STUDY among the ER positive tumors ,80.8% show low TAM infiltration, 57% show moderate infiltration and 24% show high infiltration. ER receptor positivity has good prognosis with low TAM infiltration .ER receptor status correlated with TAM density (P value -0.0005). Stina et al show similar significant correlation between ER positivity and TAM infiltration.

In present study, among HER 2 NEU positive tumors ,57% show moderate infiltration and 24% show high infiltration of TAM. HER 2 neu positive tumors are associated with poor prognosis and present with metastasis at the time of diagnosis. HER2 NEU positivity correlated with TAM infiltration (P value-0.0005). Medrek et al show HER2NEU positivity is proportional to TAM infiltration.

Among the Triple negative tumors ,56% show high TAM infiltration in the tumor. Triple negative tumors are high grade and they have aggressive clinical behaviour. Triple negative hormonal status and TAM density is correlated in present study (P value – 0.0005) Medrek et al show positive correlation between TAM density and triple negative status.

ER/PR + and HER2NEU negative tumors are moderately differentiated and respond well to hormone treatment. In our study these tumors show low macrophage infiltration 38.3%. ER/PR+H2N – status correlated with TAM density in present study (P value- 0.0005)

Triple positive tumors are of higher grade and have increased proliferating index. These tumors respond to chemotherapy. They have better prognosis than H2N and triple negative tumors. In present study 34.6% had low macrophage infiltration and 18.4% had moderate infiltration. Triple positive hormonal status correlate with TAM infiltration (P value-0.0005). Hasong et al show triple positive tumors have TAM density lower than triple negative and H2N negative tumors. Zhong et al show high TAM infiltration is seen in 35.9% of triple negative cases. Patients with high TAM infiltration had significantly increased risk for developing distant metastasis and poor outcome and disease free survival.[26]

CONCLUSION

This is a hospital based study and may not represent the true incidence of disease in community. Tumor associated macrophages are considered as poor prognostic factor and are associated with early metastasis and recurrence. TAM play an important role in “Cancer dormancy”. Expression of Tumor associated macrophages was assessed by CD163 immunohistochemical marker.

Maximum infiltration was seen in grade III tumors which show high TAM density. Among the ER,PR,HER2neu status, most of the TAMs are expressed in triple negative tumors correlating with poor prognosis.

In near future TAMs can be targeted along with standard therapies in aggressive tumors, thereby preventing recurrence and metastasis and enhancing disease free survival and quality of life.

REFERENCES

1. Bray, Freddie & Ferlay, Jacques & Soerjomataram, Isabelle & Siegel, Rebecca & Torre, Lindsey & Jemal, Ahmedin. (2018). Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries: Global Cancer Statistics 2018. CA: A Cancer Journal for Clinicians. 68. 10.3322/caac.21492.
2. Sondik EJ. Breast cancer trends. Incidence, mortality, and survival. Cancer 1994, 74:995–999.
3. Kroemer, G. et al. Natural and therapy-induced immunosurveillance in breast cancer. Nat. Med. 21, 1128–1138 (2015).
4. Koebel, C. M. et al. Adaptive immunity maintains occult cancer in an equilibrium state. Nature 450, 903–907 (2007).
5. Denkert, C. et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J. Clin. Oncol. 28, 105–113 (2010).
6. Ali, H. R. et al. Association between CD8+ T-cell infiltration and breast cancer survival in 12,439 patients. Ann. Oncol. 25, 1536–1543 (2014).
7. Mantovani, A. et al. Inflammation and cancer: Breast cancer as a prototype. The Breast (2007); 16, Supple 27–33.
8. Stavrou M, Constantinidou A. Tumor associated macrophages in breast cancer progression: implications and clinical relevance. Front Immunol. 2024 Jul 9;15:1441820. doi: 10.3389/fimmu.2024.1441820. PMID: 39044824; PMCID: PMC11263030.
9. Andreu P, Johansson M, Affara NI, Pucci F, Tan T, Junankar S, Korets L, Lam J, Tawfik D, DeNardo DG, et al. FcRgamma activation regulates inflammation-associated squamous carcinogenesis. Cancer Cell. 2010;17:121–34.

10. Kim S, Takahashi H, Lin WW, Descargues P, Grivennikov S, Kim Y, Luo JL, Karin M. Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis. Nature. 2009;457:102–6.
11. Sorokin L. The impact of the extracellular matrix on inflammation. Nat Rev Immunol. 2010;10:712–23.
12. Greten FR, Karin M. The IKK/NF-kappaB activation pathway—a target for prevention and treatment of cancer. Cancer Lett. 2004;206:193–9.
13. Kuang DM, Zhao Q, Peng C, Xu J, Zhang JP, Wu C, Zheng L. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. J Exp Med. 2009;206:1327–37.
14. Finkernagel F, Reinartz S, Lieber S, Adhikary T, Wortmann A, Hoffmann N, Bieringer T, Nist A, Stiewe T, Jansen JM, et al. The transcriptional signature of human ovarian carcinoma macrophages is associated with extracellular matrix reorganization. Oncotarget. 2016;
15. Deng YR, Liu WB, Lian ZX, Li X, Hou X. Sorafenib inhibits macrophage-mediated epithelial-mesenchymal transition in hepatocellular carcinoma. Oncotarget. 2016;7:38292–305.
16. Tomita T, Sakurai Y, Ishibashi S, Maru Y. Imbalance of Clara cell-mediated homeostatic inflammation is involved in lung metastasis. Oncogene. 2010;30:3429–39.
17. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010;141:39–51.
18. Krausgruber, T. et al. IRF5 promotes inflammatory macrophage polarization and TH1-TH17 responses. Nat. Immunol. 12, 231–238 (2011)
19. Ngambenjawong C, Gustafson HH, Pun SH. Progress in tumor-associated macrophage (TAM)-targeted therapeutics. Adv Drug Deliv Rev. 2017;114:206–221. doi:10.1016/j.addr.2017.04.010
20. Qian, B. -Z. et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature 475, 222–225 (2011).
21. Kurahara, H. et al. Clinical significance of folate receptor β–expressing tumor-associated macrophages in pancreatic cancer. Ann. Surg. Oncol. 19, 2264–2271 (2012)
22. Rogers, T. & Holen, I. Tumour macrophages as potential targets of bisphosphonates. J. Transl. Med. 9, 177 (2011).
23. Coscia, M. et al. Zoledronic acid repolarizes tumour-associated macrophages and inhibits mammary carcinogenesis by targeting the mevalonate pathway. J. Cell Mol. Med. 14, 2803–2815 (2010)
24. Dewan, M. Z. et al. Synergy of topical toll-like receptor 7 agonist with radiation and low-dose cyclophosphamide in a mouse model of cutaneous breast cancer. Clin. Cancer Res. 18, 6668–6678 (2012).
25. William F. Anderson Comparison of Age Distribution Patterns for Different Histopathologic Types of Breast Carcinoma, Cancer Epidemiol Biomarkers Prev 2006;15(10). October 2006 DOI: 10.1158/1055-9965
26. Yuan, Zhong-Yu et al. "High infiltration of tumor-associated macrophages in triple-negative breast cancer is associated with a higher risk of distant metastasis." OncoTargets and therapy vol. 7 1475-80. 21 Aug. 2014, doi:10.2147/OTT.S61838.