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Original Article

Pathology Section

Immunohistochemical Expression of Anaplastic Lymphoma Kinase in Invasive Breast Carcinomas- A Retrospective Study

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ABSTRACT

Introduction: Breast carcinoma remains one of the most common causes of mortality among female cancer patients inspite of improvements in treatment modalities. Increased survival rate can be achieved by identification of new targeted therapies. Anaplastic Lymphoma Kinase (ALK) alterations are present in many solid and haematological tumours indicating its role in pathogenesis and treatment. There are studies regarding the expression of ALK in few breast cancers but its importance was not clearly mentioned. Hence, identification of ALK overexpression in breast cancers, particularly in Triple Negative Breast Cancers (TNBC) might play a role in their chemotherapy with the help of ALK inhibitors.

Aim: To study the ALK expression in different subtypes of invasive carcinomas of breast.

Materials and Methods: This was a retrospective cross-sectional study conducted in the Department of Pathology at Great Eastern Medical School (GEMS) and Hospital, Srikakulam, Andhra Pradesh, India, from January 2022 to July 2022. The data of 60 patients, from January 2021 to December 2021 was retrieved using Hospital Information Management System (HIMS) and the Haematoxylin and Eosin (H&E)-stained slides and formalin fixed paraffin embedded tissue blocks of breast tumour were retrieved and reviewed. Estrogen receptor (ER), Progesterone receptor (PR) and Human Epidermal growth factor Receptor 2 (HER2) immunostains were performed and categorised based on molecular classification as Luminal, Her2 and Triple negative. ALK Staining was performed on all cases and its expression was studied. Statistical Package for Social Sciences (SPSS) software version 2.0 was used for analysis of data. Mean with standard deviation is used for quantitative variables and prevalence, ratio is used for quantitative variables. Chi-square test and Fischer exact test were used for detecting significance. The p-value <0.05 was considered as significant.

Results: Out of 60 cases, majority (N=22; 36.66%) of patients were in the age group of 51-60 years. The mean tumour size was 3.2±0.5 cm. The most common histological type was invasive breast carcinoma, No Special Type (N=44; 73.34%). Majority of the tumours showed grade 1 and 2 with 24 (40%) and 25 (41.67%) cases, respectively. A total of 30 cases (50%) of tumours belonged to stage T2. Luminal molecular subtype was the most common 31 (51.67%) cases followed by TNBC, 16 (26.67%) cases and Her2neu 13 (21.67%) cases. Among all the cases, ALK overexpression was seen in 17 (28.33%) cases and among different molecular subtypes, its expression was seen in 5 (8.33%) cases of Luminal type, 3 (5.0%) cases of HER2 type and in 9 (15.0%) cases of TNBC cases.

Conclusion: Immunohistochemical analysis showed ALK over expression in a substantial proportion of cases and possibly plays a significant role in aggressive behaviour of breast cancer. ALK inhibitors offer an opportunity to treat aggressive subtypes of breast cancer.

Keywords: Aggressive, Biomarker, Chemotherapy, Pathogenesis, Triple negative breast cancer

INTRODUCTION

Breast carcinoma is the most common malignant tumour and the leading cause of carcinoma death in women [1], with more than 1.7 million cases occurring worldwide annually [2]. According to Globocan data 2020, breast cancers accounted for 13.5% (N=178361) of all cancer cases and 10.6% (N=90408) of all deaths with a cumulative risk of 2.81 [3] in India. The incidence risk increases its peak, by the time they reach 50-64 years of age [3]. Estimated new cases of breast cancer in 2021 is 2,81,550 with 14.8% accounting to all new cancers in India [3].

Breast carcinomas arise from the same segment of the Terminal Duct Lobular Unit (TDLU) [4]. Early diagnosis by clinical examination, screening by mammography, ultrasonography and Magnetic Resonance Imaging (MRI) are essential in identifying high-risk cases [5]. Thereby confirmation with fine needle aspiration and needle core biopsy is necessary for prompt diagnosis [5]. The genetic and epigenetic mutations that deregulate oncogenic pathways that initiate a more aggressive breast cancer phenotype [6,7]. Hence, molecular categorisation of breast cancer plays a role in treatment and prognosis, signifying the importance of Immunohistochemistry (IHC) and subtyping [8].

Triple Negative Breast Cancers (TNBC) have the worst prognosis amongst all the subtypes of breast cancer [9,10]. The Anaplastic Lymphoma Kinase (ALK) stimulates various signalling pathways i.e. Signal Transducer and Activator of Transcription 3 (STAT3), AKT/PI3K (phosphatidylinositol 3-kinase) and RAS/ERK (Extracellular signal-regulated kinase) and plays a major role in pathogenesis of many malignant tumours by encoding a transmembrane tyrosine kinase receptor, thereby causing increased cellular proliferation, cell migration and survival [11]. It was originally discovered as the underlying factor in the pathogenesis of Anaplastic Large Cell Lymphomas (ALCL) [12].

The ALK Tyrosine Kinase Receptor (TKR) has emerged recently as a potentially relevant biomarker and therapeutic target in solid and haematologic tumours [13]. ALK alterations are present in 80% of inflammatory breast cancer and 25% of Triple Negative Breast Cancers (TNBC), which are most aggressive subtypes of breast cancers [14]. ER positive cases are treated with selective estrogen receptor modulators like Tamoxifen, Raloxifene, aromatase inhibitors, while, the drugs of choice for HER2 positive cases are Transtuzumab, Pertuzumab, Taxane, etc. But, for TNBC cases, there is no specific hormone therapy and relies only on chemotherapy [15].

Since TNBC have poor prognosis among various breast cancers and lacks any molecular target, thus identifying ALK overexpression can be exploited as a potential therapeutic target [16] in the management of aggressive breast cancer and helps in improved survival with the help of ALK inhibitors.

The purpose of this study was to know the Immunohistochemical (IHC) expression of ALK in different breast cancer subtypes with special emphasis on TNBC. The objectives of the study were to evaluate the distribution of various clinicopathological parameters in invasive breast cancers, to study the ALK (IHC) expression in histopathological and molecular subtypes of breast cancers and to know the significance of ALK expression in TNBC, by reclassifying molecular subtypes into TNBC and Non TNBC.

MATERIALS AND METHODS

This was a cross-sectional retrospective study of breast cancers, conducted in the Department of Pathology at Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India from January 2022 to July 2022. This study was approved by the Institutional Ethical Board (IEC:11/2022).

Inclusion criteria: Slides and blocks having patient details related to all invasive breast carcinomas during the above the mentioned period were included in the study.

Exclusion criteria: Those cases where neither slides/blocks nor patient details available, blocks with inadequate tissue, slides with non representative material and incisional biopsies were excluded from the study.

Sample size calculation: Was done by confidence interval of 95%, marginal error of 5% and population proportion as 4%.

Study Procedure

The clinical (age and gender) and histopathological (tumour size, histological type, grade, stage, IHC for ER, PR and HER2) data of breast cancers for a period of one year i.e., from January 2021 to December 2021 were retrieved using Hospital Information Management System. Haematoxylin and Eosin (H&E) Slides and Formalin Fixed Paraffin Embedded (FFPE) tissue blocks of breast tumours were retrieved. The histologic subtype of each breast tumour sample was classified according to World Health Organisation (WHO) criteria [17]. Grading of the tumours was done based on scores for tubular differentiation, nuclear pleomorphism and mitotic rate as Grade 1 (for total score 3-5), Grade 2 (for total score 6-7) and Grade 3 (for total score 8-9) [17]. Staging of the tumours were done according to College of American Pathologists (CAP) protocol based on tumour size and extension, nodal and distant metastasis [18]. The slides from tumour proper of resected specimens were reviewed and hormonal status (ER, PR, HER2) were categorised as Luminal, Her2 and Triple Negative according to molecular classification [19]. Luminal type includes ER positive and HER2 negative tumours, HER2 type includes HER2 positive tumours and TNBC includes tumours which are negative for ER, PR and HER2.

The ALK immunohistochemical staining was performed on all invasive breast carcinoma cases, using standard laboratory protocols [20] by using anti-human CD246ALK antibody (clone ALK1, Ready to use, Dako). Tumours having cytoplasm and/or nuclear staining in more than 10% of tumour cells are considered as positive whereas tumours with ≤10% are considered as negative [12]. Sections of immunohistochemically confirmed anaplastic large cell lymphoma blocks were taken as positive controls and negative controls by omitting the primary antibody.

STATISTICAL ANALYSIS

The SPSS software version 20.0 was used for all statistical analysis. For quantitative variables, mean and standard deviation were used and for qualitative ones, prevalence and ratio were used. Chi-square test, Fisher exact test were used to detect significance, 2-sided significance for each was considered. All p-values of <0.05 resulting from two-sided tests were considered significant.

RESULTS

Total 60 female breast cancer patients were studied with age range between (29-70 years) [Table/Fig-1] and mean age of 51 years±11.6 years. Tumour sizes ranged from 1-9 cm with a mean of 3.2±0.5 cm. Invasive ductal carcinoma of no special type is the most common histological subtype, constituted N=44 (73.34%) of all the studied cases, followed by invasive lobular carcinoma (N=5; 8.34%), medullary (N=4; 6.67%), papillary (N=3; 5.0%), metaplastic (N=2; 3.34%), secretory and adenoid cystic carcinoma (N=1; 1.67%) [Table/Fig-2].

Age (Years)	Number of cases	Percentage (%)
21-30	2	3.33%
31-40	11	18.33%
41-50	16	26.66%
51-60	22	36.66%
61-70	9	15.0%
Total	60	100%

[Table/Fig-1]: Distribution of age of the patients.

Parameters	Number (N)	Percentage (%)
Mean age (years)	51+11.6	
Mean tumour size (cm)	3.2+0.5	
Histological type		
• No special type	44	73.34%
• Lobular	5	8.34%
• Medullary	4	6.67%
• Papillary	3	5.0%
• Metaplastic	2	3.34%
• Secretory	1	1.67%
• Adenoid cystic carcinoma	1	1.67%
Grade		
• 1	24	40.0%
• 2	25	41.67%
• 3	11	18.33%
Tumour status		
• T1	8	13.33%
• T2	30	50.0%
• T3	14	23.34%
• T4	8	13.33%
Nodal status		
• N0	8	13.33%
• N1	24	40.0%
• N2	20	33.34%
• N3	8	13.33%

[Table/Fig-2]: Distribution of clinicopathological parameters.
Total N=60 patients

With respect to tumour grading, grade 2 constituted the majority of the cases (N=25; 41.67%) while grade 1 was 24 cases (40.0%) and grade 3 were 11 (18.33%) cases. As regards tumour stage, 8 (13.33%) cases were T1, 30 (50.0%) cases were T2, 14 (23.34%) cases were T3 and 8 (13.33%) cases were T4. Fifty-two cases had lymph node metastasis (86.67%), in which N1 were 24 (40.0%) cases, N2 were 20 (33.34%) cases and N3 were 8 (13.33%) cases [Table/Fig-2].

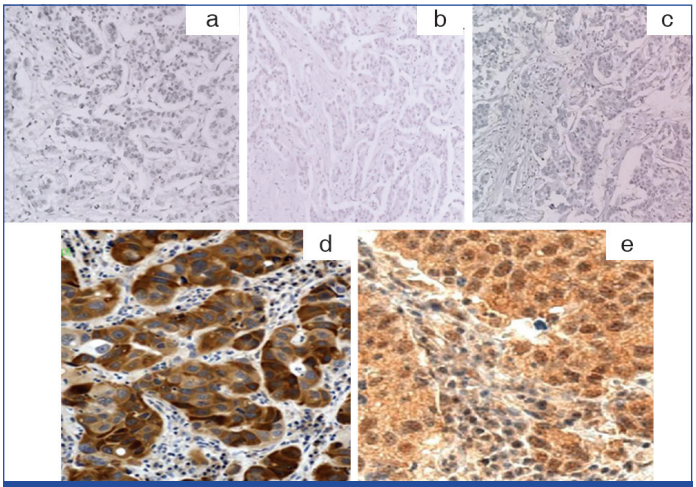
Based on molecular subtyping, 31 (51.67%) cases were of Luminal type, 16 (26.66%) cases were triple negative and 13 (21.67%) cases were Her-2 enriched [Table/Fig-3].

Out of the total 60 cases, 17 (28.33%) cases showed positive expression for ALK in malignant epithelium. In all these 17 cases, ALK is expressed as diffuse cytoplasmic positivity in more than 10%

Molecular subtypes	Number (N)	Percentage (%)
Luminal	31	51.67%
Her2 +ve	13	21.67%
TNBC	16	26.66%
Total no. of cases	60	100%

[Table/Fig-3]: Molecular classification of breast carcinoma cases.
TNBC: Triple negative breast cancers; HER2: Human epidermal growth factor receptor 2

of the tumour cells [Table/Fig-4]. Some of the tumour cells showed positivity in cytoplasm as well as in the nucleus of the tumour cells [Table/Fig-4]. Among all histological subtypes, ALK is found to be significantly expressed in NST type (N=8;13.33%) (p-value=0.0079) [Table/Fig-5]. Among the ALK positivity for molecular subtypes, 5 cases (8.33%) were Luminal type, 3 (5.0%) were Her 2+ve and 9 (15.0%) were Triple negative [Table/Fig-6]. When molecular subtypes were reclassified into TNBC and Non TNBC, ALK is significantly not expressed in Non TNBC (p-value=0.0079) [Table/Fig-4,7].



[Table/Fig-4]: Immunohistochemical Anaplastic Lymphoma Kinase (ALK) expression in TNBC.
Immunostaining of a TNBC case showing Negativity for ER (IHCx100, 4A), PR (IHCx100, 4B), Her2 (IHCx100, 4C), but cytoplasmic positivity for tumour cells when Immunostained with ALK (IHCx400, 4D). Another case of TNBC showing cytoplasmic and nuclear positivity for tumour cells when Immunostained with ALK (IHCx400, 4E)

Histological subtypes	ALK expression (Positive)		ALK expression (Negative)		p-value
	Number (N)	Percentage (%)	Number (N)	Percentage (%)	
NST	8	13.33%	36	60.0%	0.0079
Lobular	2	3.33%	3	5.0%	0.6159
Medullary	3	5.0%	1	1.67%	0.0648
Papillary	2	3.33%	1	1.67%	0.1908
Metaplastic	1	1.67%	1	1.67%	0.4898
Secretory	1	1.67%	0	0%	0.2833
Adenoid cystic	0	0%	1	1.67%	1.00

[Table/Fig-5]: ALK expression in different histologic subtypes of breast carcinoma.
Chi-square test used for ALK expression in histological subtypes showing significant expression of ALK for No Special Type (NST) (p=0.0079)

Molecular subtypes	Number (N)	Percentage (%)
Luminal	5	8.33%
Her2 +ve	3	5.0%
TNBC	9	15.0%
Total no. of cases	17	28.33%

[Table/Fig-6]: ALK expression in molecular subtypes of breast carcinoma.

DISCUSSION

The role of ALK in disease progression and treatment is well documented in many tumours but not so in breast carcinomas. Evaluation of established biomarkers ER, PR and HER2 in invasive

Molecular subtype	ALK positive		ALK negative		p-value
	Number (N)	Percentage (%)	Number (N)	Percentage (%)	
Non TNBC	8	18.18%	36	81.82%	0.0079
TNBC	9	56.25%	7	43.75%	

[Table/Fig-7]: Comparison of ALK expression in TNBC and Non TNBC.
Fischer exact test used for ALK expression in TNBC and Non TNBC and found that ALK is significantly expressed in TNBC and not expressed in Non TNBC (p=0.0079)

breast carcinomas is considered as standard of care in view of availability of endocrine therapy, if these biomarkers are expressed in the tumours. But there is no definitive endocrine therapy for the TNBC i.e., which are negative for ER, PR and HER2. The present study was an attempt to identify the IHC expression of ALK in invasive breast carcinomas, given the availability of ALK inhibitors and it was found that ALK was expressed in a small but significant number of cases, particularly in TNBC cases, indicating its role in pathogenesis and therapy. Breast cancers evolve through variable genetic and epigenetic mutations into more aggressive breast cancer phenotypes, hence identifying these mutations play a significant role in development of novel target therapies which can improve the quality of life of the suffering [21].

The present study demonstrated positive expression of ALK in 17 out of 60 cases (28.3%), out of which, 5 cases (29.4%) were Luminal type, 3 (17.7%) were Her 2+ve and 9 (52.9%) were Triple negative. Similar kind of ALK expression was observed by Bassam AM et al., [22] with 29.5% of total breast cancer cases. This was in contrast to Perez-Pinera P et al., [23], who observed ALK expression in all breast cancer cases. This discordance in present study might be related to altered mutagenesis and growth of abnormal clones which are variable with different geographic locations, lifestyle factors or by differences in tissue fixation, processing, immunohistochemical processing and different kinds of antibody used for detection of ALK protein.

There are significant differences in the patterns of ALK expression in breast cancer and in normal breast [23]. Present study revealed cytoplasmic staining in all positive cases with five cases showing concomitant cytoplasmic and nuclear immunoreactivity. This was in concordance with Bassam AM et al., [22] who observed eight cases with concomitant cytoplasmic and nuclear immunoreactivity. In the present study, ALK expression was observed in some of the cases in nucleus of normal breast epithelium. This was in concordance with Bassam AM et al., [22] Pinera P et al., [23] who also observed similar kind of ALK expression. This indicates that cytoplasmic localisation of ALK expression in malignant epithelium may be due to amplification or mutation leading to aberrant ALK expression. This was contradictory when compared with Mehrjardi AM and Vaghefi A, [21] where they described the distribution of ALK in normal breast epithelial cells to be localised to the cytoplasm. This needs further studies for evaluating and correlating different aberrant molecular alterations associated with epigenetic and genetic pathways leading to overexpression of ALK and might be reason of various patterns of cytoplasmic, nuclear and cell membrane immunoreactivity.

Mehrjardi AM and Vaghefi A, [21] found no relationship between ALK expression and clinicopathological parameters like patient's age, tumour type and grade, necrosis, vascular invasion, skin involvement, lymph node metastasis and status of hormone receptors.

The ALK alterations appear as a molecular tumourigenic event in many tumours (ALKomas) like non small cell lung cancer, Anaplastic large cell lymphoma, Neuroblastomas, Inflammatory myofibroblastic tumours, many solid and haematological tumours implicating its role in pathogenesis of aggressive tumours. Hence identification of ALK expression in these tumours is important, as it offers a therapeutic target with help of ALK inhibitors [23]. The ALK tyrosine kinase inhibitors like crizotinib, which acts against ALK kinase domain, found to have therapeutic role in clinical trials [24-26]. These ALK

alterations may also be responsible in the pathogenesis of aggressive breast cancers, Hence, if ALK can be detected, particularly in aggressive cancers like TNBC, may have a therapeutic value.

The present study showed, ALK expression predominantly in NST histological type (13.33%) and in TNBC (15%). So, in these aggressive triple negative breast cancers, ALK inhibitors can be of paramount value and may significantly improve the prognosis. AK Siraj et al., [14] demonstrated that ALK protein was overexpressed in 47 % of TNBC cases similar to the present study with 52.9% of all TNBC cases. Further in the present study, it is found that when molecular subtypes were divided into TNBC and Non TNBC, ALK is significantly not expressed in Non TNBC, which shows the role of ALK in pathogenesis of aggressive TNBC.

Limitation(s)

Because of the smaller sample size, influencing factors for development are not well established. Prospective studies with larger sample size including racial, geographical, environment factors along with more specific methods of ALK detection like in-situ hybridisation, PCR and follow-up of patients treated with ALK inhibitors are needed for their implementation in breast cancer chemotherapy.

CONCLUSION(S)

The ALK inhibitors has well established role in the treatment of many malignancies which are immunohistochemically positive for ALK. Its expression is also identified in a significant number of invasive breast carcinomas. Among the different histological subtypes, ALK is predominantly expressed in NST type, while in molecular subtypes, it is predominantly seen in TNBC. Hence, ALK inhibitors can be of therapeutic value in these subsets of cases, particularly for TNBC where there is no specific hormonal therapy. However, these findings have to be substantiated by larger studies with survival data.

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