ISSN: 2789-4622 (print)
ISSN: 2789-4630 (online)

CANCER JOURNAL OF BANGLADESH

Cancer J Bangladesh. Vol. 2, No. 2: July 2021
www.nicrh.gov.bd

CONTENTS

AN OFFICIAL JOURNAL OF TEACHERS' ASSOCIATION OF
NATIONAL INSTITUTE OF CANCER RESEARCH & HOSPITAL (NICRH)

CANCER JOURNAL OF BANGLADESH

Vol. 2, No. 2, July 2021

The Official Journal of the Teacher's Association of
National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh
www.nicrh.gov.bd

The "Cancer Journal of Bangladesh" is a peer reviewd medical journal of the National Institute of Cancer Research & Hospital, Dhaka, Bangladesh. It is published twice a year, January and July. It accepts original articles, review articles and case reports of scientific merits related to cancer.

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Published by

Professor (Dr.) Qazi Mushtaq Hussain on behalf of the Teachers' Assocaiton of NICRH

Printed at:

Asian Colour Printing
130, DIT Extension Road, Dhaka, Bangladesh
Phone: 49357726, 58313186, E-mail: asianclr@gmail.com

Subscritption

Tk 200 or $ 30 per copy

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The 'Cancer Journal of Bangladesh' is a peer reviewed medical journal published by the National Institute of Cancer Research & Hospital, Dhaka, Bangladesh. It is published twice a year, January and July. It accepts original articles, review articles and case reports and short communications of scientific merits related to cancer.

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ISSN: 2789-4622 (print)
ISSN: 2789-4630 (online)

CANCER JOURNAL OF BANGLADESH

Cancer J Bangladesh. Vol. 2, No. 2, July 2021
www.nicrh.gov.bd

CONTENTS

Editorial

Cancer J Bangladesh 2021;2(2): 1-2
http://nicrh.gov.bd/publication

Global Strategy for Cervical Cancer Elimination

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Citation: Anwar BR. Global Strategy for Cervical Cancer Elimination. Cancer J Bangladesh 2021;2(2):1-2.

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In 2018, an estimated 570 000 cases of cervical cancer were diagnosed, and 311 000 women died from the disease.[1] Although cervical cancer has been relatively well controlled for several decades in many high-income countries, mainly because of cervical screening initiatives and effective cancer treatment services, it remains the most common cause of cancer related death among women in 42 countries, most of which are low income and lower-middle- income countries.[2] In 2018, the Director-General of World Health Organization (WHO) announced a call to action towards elimination of cervical cancer. In January 2019, the Executive Board of the WHO requested a draft strategic plan be prepared for discussion at the World Health Assembly in May 2020. Thus, major efforts are being made to define scaled-up targets for interventions, the elimination threshold for cervical cancer, and to evaluate vaccine, screening and treatment technologic supply pipelines, and mechanisms for effective delivery of these interventions in LMIC.[3]

The draft strategic plan, WHO has defined global "90/70/90" targets as follows- by 2030, 90% of young adolescents will be vaccinated with HPV vaccine by 15 years of age. 70% of women will be screened with high-performance test (HPV test) at least twice (by age 35 and 45) in their lifetime, and 90% of women will be effectively treated for precancerous lesions or management of 90% of invasive cancers, with effective palliation also a priority for women with advanced cervical cancer. The draft threshold for considering cervical cancer eliminated as a public health issue is 4 per 100,000 women per annum. Modeling has predicted that achieving high levels of scaled-up vaccination, combined with cervical screening, has the potential to avert up to 12.5 to 13.4 million cervical cancer cases in next half century.[4]

Increased awareness, and dissemination, use and scale-up of these recommendations will improve equity, increase access to services, and improve the health of women and play a significant role in reducing the burden of cervical cancer in countries around the world.

WHO Global target "90/70/90", Challenges and situation of Bangladesh.

Prophylactic vaccines against oncogenic HPV have been available in most – high income countries from 2006 onwards. Vaccine coverage in LMICs has been low overall, with an estimated 118 million women had been targeted, but only 1% from low income or lower middle-income countries.[5] By 2016, only 14% of LMICs had established vaccination program.[6] Currently HPV vaccines are not available in Bangladesh. Government of Bangladesh by the ministry of health, with support from the Global Alliance for Vaccines and immunization (GAVI) has decided to vaccinate 10-year-old girls in the primary school setting (grade 5) with two doses of

vaccine, given 6 months apart. The target girls will mainly be reached through the school- based program and girls who are out of school will receive the vaccine through the routine EPI sites at community level [7], the program yet to be established. Hopefully vaccines will be available within 2022-2023.

Second strategy of WHO advocates that 70% of women are to be screened with a high-performance test (HPV DNA test) by 35 and 45 years of age. In low-and middle–income countries (LMICs), it is estimated that fewer than 20% of women have been screened for cervical cancer compared with 60% in high- income countries. Visual inspection with the aid of acetic acid (VIA) is the method of national cervical screening program in Bangladesh from 2005-2021. Currently the population coverage of VIA is 12.73%.[8] Recommended high precision test (HPV DNA test) is only available at National Institute of Cancer Research Hospital (NICRH) and Bangabandhu Sheikh Mujib Medical University (BSMMU). Due to high cost (20 dollars) and lack of availability of the test in primary health care center, it remained out of reach of the poor women.

Third strategy: Treatment of pre invasive and invasive cancers and provision of palliative care. 90% of women identified with pre invasive and invasive cervical cancer properly managed. Inadequate training and expertise in the field of colposcopy, difficulties in maintenance of colposcope, LEEP and cryotherapy machine leads to treatment of precancerous lesion, a real challenge for Bangladesh. The facilities are available at tertiary centers and some selected districts only.

Early-stage cervical cancer has cure rates of e" 90% when treated appropriately. In 2019, only 30% of low-income countries reported having the required diagnostic and treatment infrastructure (advanced imaging, pathology, surgery, chemotherapy, radiotherapy) available in the public health system, compared to 90% in high income countries.[9] In Bangladesh 80% of women present with advance stage (Stage III-IV) cervical cancer.[10] Radiation therapy is an extremely limited resource in Bangladesh with only one machine per over 10 million people. Only 11.2% get access to radiation therapy treatment.[11]

Important issue is that, except hospital-based registry at NICRH, the country has no population-based cancer registry. As such accurate data of cervical cancer and precancerous lesions are unavailable. Therefore, development of cervical cancer data base in whole country is the utmost priority to detect number and location of screened and unscreened women, availability of treatment of pre invasive and invasive cervical cancer, access to radio therapy machine to treat advance cancer.

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Original Article

Cancer J Bangladesh 2021;2(1): 3-6
http://nicrh.gov.bd/publication

Diagnostic Work-up of Early-Stage Breast Cancer: Our Current Practice

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Citation: Alam S, Sayed MMA, Haque MN, Rahman MA, Siddiqua A. Diagnostic work-up of Early-Stage Breast Cancer: Our Current Practice. Cancer J Bangladesh 2021;2(2): 3-6.

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Received : 09 August 2021
Accepted : 01 September 2021
Published : 08 November 2021

Abstract

Background: *The breast cancer diagnosis is based on a triple diagnostic approach consisting of clinical examination in combination with imaging and confirmed by pathological assessment. Besides a complete history & physical examination, guidelines have made recommendations regarding workup. This observational study was carried out to see how early-stage breast cancer patients were evaluated and diagnosed in our country.* ***Materials and method:*** *A retrospective review of medical records of 109 patients with early-stage breast cancer referred to the Tumor Board and Radiation Oncology department of National Institute of Cancer Research & Hospital, who were diagnosed & evaluated either in NICRH or outside during September 2018 to September 2019 were performed to determine how they were diagnosed and evaluated.* ***Results:*** *Regarding imaging of the breast, 20 patients (18.3%) had no pre-operative imaging. Bilateral USG of breasts was done in 74 patients (67.8%). A bilateral diagnostic mammogram was done in 33 patients (30.3%). Both USG of breasts & mammograms were available in 29 patients (26.6%). In pathology review, FNAC was performed in 97 patients (89%) and core biopsy in 34 patients (31%). Both FNAC & core biopsy were performed for 26 patients (23.9%). Excision biopsies were done in 13 patients (12.0%), among which 9 cases were following a negative FNAC. Hormone receptor & HER2 status were available in 101patients (92.6%), of which 17 (15.6%) were done preoperatively.* ***Conclusion:*** *According to the current standard of care, we have to emphasize preoperative bilateral breast imaging, core biopsy, and hormone and HER2 receptor status study.*

Key words: *Early-Stage Breast Cancer, current practice, Bangladesh*

Introduction:

Worldwide breast cancer is the most frequently diagnosed cancer and a leading cause of cancer deaths among females, accounting for 25% of cancer cases and 15% of cancer deaths.[1] Although breast cancer has traditionally been less common in non-industrialized nations, its incidence in this area is increasing.[1]

According to the Hospital Cancer Registry Report, 2015-2017 of the National Institute of Cancer Research

& Hospital, Dhaka, breast cancer is the top most cancer in females accounting for 30.4% of all female cancers and the second most common malignancy in both sexes combined (14.1%) among all the cancer patients treated in NICRH from January 2015- December 2017.[2]

Cancer of the breast represents a wide spectrum of disease with a variety of clinical, biological and genetic characteristics resulting in a considerable variation in outcome and prognosis. Optimal management of breast cancer needs timely diagnosis, proper staging, adequate surgery and adjuvant therapies either alone or in combination depending on prognostic factor evaluation.

TNM stages I & II are the early stage of invasive breast cancer and traditionally operable stages. Together they constitute 75% to 80% of all cases of breast cancer in developed countries where screening mammogram has been adopted.[3] As there is no population-based cancer registry in Bangladesh, we do not actually know the percentage of early-stage breast cancer. According to the surgical audit 2018 by the Department of Surgical Oncology, NICRH, it has been shown that 34% of patients presented in the early stage of breast cancer.[4]

The diagnosis of breast cancer is based on a triple diagnostic approach consists of clinical examination in combination with imaging and confirmed by pathological assessment. Evaluation of the tumor extent, multi-centricity, synchronous primary in the opposite breast, nodal status, tumor type & biology before surgery are standard of care. Besides a complete history & physical examination for clinical staging, according to the NCCN guidelines, the recommended workup of early-stage breast cancer includes bilateral diagnostic mammogram; USG of bilateral breasts and axilla; pathological reviews include Core needle biopsy of a suspicious breast lump and percutaneous biopsy of suspicious lymph nodes, determination of tumou Estrogen, progesterone receptors and HER 2 statuses. Breast MRI is not routinely recommended. Routine systemic imaging is not indicated for patients with early-stage breast cancer in the absence of significant symptoms of metastatic disease.[5-8]

NICRH having all the facilities of multi-disciplinary management of breast cancer has become the largest service provider to breast cancer patients all over the country. Department of Radiation Oncology NICRH is the only government center having four linear accelerator machines, providing radiotherapy to the highest number of breast cancer patients of Bangladesh yearly who receive their surgery and chemotherapy either in NICRH or outside. The data of breast cancer patients treated in NICRH truly reflects the demography, clinicopathological characteristics, how breast cancer patients are diagnosed and evaluated all over Bangladesh.

Materials and method:

A retrospective review of medical records of 109 patients with early-stage breast cancer referred to the Tumor board and Radiation Oncology department of NICR&H who were diagnosed either in NICR&H or outside during September 2018 to September 2019 were performed to determine how they were and evaluated and diagnosed.

Results:

Among the 109 cases available for review, based on pathological staging, five patients (4.6%) were in stage 0, nineteen patients (17.4%) were in stage IA, fifty-two patients (47.7%) were in stage IIA & thirty-three patients (30.3%) were in stage IIB. The median age at diagnosis was 45.0 (SD ± 10.33) years. Regarding imaging of the breast, 20 patients (18.3%) had no pre-operative imaging. Bilateral USG of breasts were done in 74 patients (67.8%) & USG of the only involved breast was done in 11 patients (10.1%). A bilateral diagnostic mammogram was done in 33 patients (30.3%). Both USG of breasts & mammograms were available in 29 patients (26.6%). In pathology review, FNAC was performed in 97 patients (89%) and core biopsy in 34 patients (31%). Both FNAC & core biopsy were performed for 26 patients (23.9%). Regarding the interpretation of FNAC, in 68 patients (70%) it was concordant with post-operative HPR report, in 13 patients (13%) it was a false negative, in 12 patients (12%) results were suspicious and in 4 patients (4%) post modified radical mastectomy HPR came out as ductal carcinoma in situ, which were invasive ductal carcinoma according to FNAC. Excision biopsies were done in 13 patients (12.0%) among which 9 cases were following a negative FNAC. Four patients were diagnosed with cancer after an unplanned lumpectomy. FNAC of a suspicious axillary node was done only in 5 patients. Hormone receptor & HER2 status were available in 101patients (92.6%), of which 17 (15.6%) were done preoperatively & 84 (77%) postoperatively.

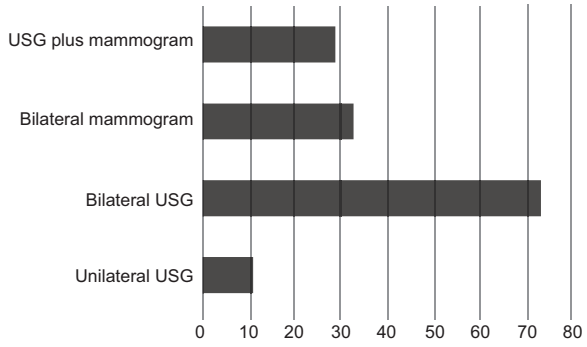

Fig.-1: *Preoperative imaging of breast*

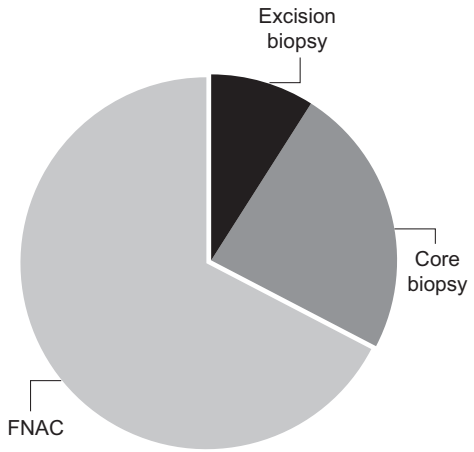

Fig.-2: *Methods of pathology review*

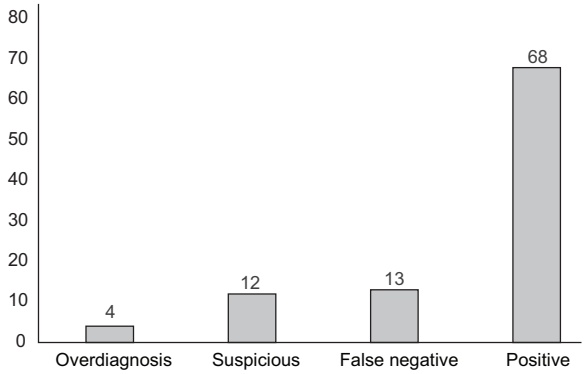

Fig.-3: *Interpretation of FNAC*

Discussion:

The majority of patients with early-stage of breast cancer present with painless or slightly tender breast mass or have an abnormal screening mammogram. The workup of a patient with breast mass includes complete history taking and a triple diagnostic approach, which consists of breast inspection and palpation, breast imaging usually with bilateral diagnostic mammography and breasts and axillary ultrasound, and a core needle biopsy of the breast lesion. Breast imaging should precede a biopsy, since a haematoma or other tissue alterations may interfere with image interpretation.

A diagnostic mammogram is a definitive imaging workup and a problem-solving consultative examination designed to evaluate an abnormality detected with a screening mammogram or physical examination which includes supplementary views. It can provide important information about the likelihood of malignancy, size, site, multicentricity or multifocality and also gives information about the synchronous primary of the opposite breast.

Ultrasound has become the most important adjunctive study to mammograms and is a vital part of workup in many breast abnormalities. It has been used preliminary to distinguish cystic from a solid lesion, for evaluation of axilla. Perhaps the area of most significant change is that of the image-guided biopsy. But with USG it is possible to confuse small cancers with fibroadenomas, to miss diffusely infiltrating malignancies and to fail to detect suspicious microcalcifications. Rubin & others [9] found USG to be a useful adjunct to mammography in three groups of patients: 1. patients with dense breast and localized symptoms or with a suspicious area detected on mammogram 2. patients with nonpalpable abnormalities discovered on mammogram & 3. those with palpable mass considered indeterminate on a mammogram.

But the results of each ultimately requires confirmation with histological examination. The presence or absence of malignancy can only be reliably determined by tissue biopsy. Available biopsy techniques include Fine-needle aspiration (FNA), Core needle biopsy and excisional biopsy. FNA or core biopsies are preferred because they are cost-effective and because most breast lesions are benign, they avoid a surgical scar & potential cosmetic deformity.

FNA is easily performed but requires a trained cytopathologist for accurate specimen interpretation. It cannot reliably distinguish invasive cancer from DCIS. In contrast, core needle biopsy provides a histological specimen suitable for interpretation by any pathologist. It facilitates Estrogen, Progesterone& HER2 receptor

testing which have become a critical component of Neoadjuvant treatment planning and allows for placement of a clip. The use of core biopsy is cost-effective & increases the likelihood that the patient will be able to undergo a single surgical procedure for definitive cancer treatment.[10] Excision biopsy as a diagnostic technique should be reserved for patients with imaging abnormalities that cannot be targeted for core biopsy.

The purpose of breast cancer staging is to convey a consistent method for understanding the extent of disease, prognosis & guiding the therapeutic decision. Extensive staging evaluations to look for metastatic disease are not warranted in asymptomatic patients with stage I & II breast cancers because of the low likelihood of identifying metastatic disease.[6-8]

Conclusion:

According to the current standard of care, we have to give more emphasis on the preoperative bilateral diagnostic mammogram, ultrasonogram of breasts and axilla, core biopsy of suspected breast mass and hormone and HER2 receptor status study. In the early stage of breast cancer, clinical staging is still considered to be the most useful and cost-effective.

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Original Article

Cancer J Bangladesh 2021;2(2): 7-10
http://nicrh.gov.bd/publication

HPV DNA Test: A Promising Solution to Combat Cervical Cancer

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Citation: Anwar BR. Ara N, Afroz M, Tarannum T,Ara N, Afsara A, , Islam MJ. HPV DNA Test: A Promising Solution to Combat Cervical Cancer. Cancer J Bangladesh 2021;2(2): 7-10.

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Received : 21 August 2021
Accepted : 03 September 2021
Published : 08 November 2021

Abstract

Background: *Human papilloma virus (HPV) a high risk genotype infection that influences the development of invasive cervical cancer (CC) and cervical intraepithelial neoplasia (CIN). A small percentage of women with high-risk HPV (HrHPV) infection would progress into pre-cancerous lesion, while fewer women would progress to invasive cancer. HPV DNA testing for screening of CC plays an important role in early detection and management of CIN II, CIN III and invasive cancers.* ***Objective:*** *The aim of this study was to detect individuals' positive for HrHPV, thereby evaluating feasibility of HPV DNA test as a primary screening procedure.* ***Methodology:*** *PCR based assay of HPV DNA was done in women who came for opportunistic screening. HPV 16/18 were evaluated by colposcopy and biopsy.* ***Results:*** *In total 153 individuals were screened. More than 21% (33) cases were positive for HPV DNA (both 16/18 and non 16/18 HPV). Eight-point four nine percent (n=13) were positive for 16/18 and 13% (20) were positive for HPV non 16/18. CIN-I was found in 54% (7) and CIN-II in 15% (2) confirmed by biopsy. 31% (4) of those detected as positive for HPV16/18, were colposcopically and histopathologically normal. Most of those aged beyond 30 years, were positive for 16/18. Seventy-eight percent (120) cases were HPV negative; assurance was given as they have no threat to develop CC within 5 years.* ***Conclusion:*** *CC screening by HrHPV DNA test identifies women who currently have high grade cervical lesion and are at greatest risk of developing the invasive disease in future. Hence, low and middle income countries (LMICs) needs to consider HrHPV test as primary screening test.*

Key words: *cervical cancer, HPV DNA test, screening test*

Introduction

Human papilloma virus (HPV) is considered as the main cause of most cervical cancers and cervical intraepithelial neoplasia (CIN).[1] An important public health challenge for the prevention of cervical carcinoma. HPV DNA testing has emerged as a new option for cervical cancer screening. A single round of HPV testing was associated with 50% reduction in cervical cancer incidence and mortality, whereas VIA or Pap had little effect on outcomes.

The goal of cervical cancer screening is to prevent cervical cancer. This is achieved by detection, treatment and follow-up of precancerous lesions. Understanding of HPV virus has led to important new approaches to primary and secondary cervical cancer prevention via prophylactic HPV vaccination among adolescent boys and girls and primary HPV based screening.

HPV vaccination programs have been introduced in high-income and middle-income countries, but HPV vaccine introduction in low-middle income countries (LMICs) remain insufficient. Therefore, secondary prevention with early, low-cost, high-quality HPV DNA screening is essential to reduce mortality and morbidity from cervical cancer (CC) in LMICs. Vaccination does not clear existing HPV infection. Primary HPV testing will be the standard testing in future to simplify screening in post vaccination era.

High rates of false negative results remain a major limitation of conventional cytological screening too. Detection of HPV in a cervical swab greatly improves the sensitivity of the traditional Pap test to identify high grade CIN.

It allows safe extension of screening interval of 5 years. The HPV testing with high negative predictive value has opened the door for alternative surveillance to routine screening test.

Cervicovaginal HPV DNA self-sampling is a highly acceptable method for the purpose of cervical cancer screening. It has been associated with improved participation of unscreened women in cervical cancer screening in LMICs.[2]

The possibility of relapse of cervical cancer is high during the initial two years of complete treatment. One-fourth of treated cases experience central pelvic recurrence after chemo radiation. Systemic review and meta-analysis show a greater likelihood of relapse in cervical cancer cases with persistent high-risk HPV (HrHPV) infection.[3] Annual HPV testing during the initial two years of follow up may facilitate early recognition of recurrence in cervical cancer survivors.[4]

Methods:

The present study was to detect individuals' positive for hrHPV, thereby evaluating feasibility of HPV DNA test as a primary screening procedure. Relation of HPV 16/18 type with different types of cervical lesions. The study was conducted among 153 women attended for CC screening from August 2020 to June 2021in a private clinic. PCR based assay of HPV DNA was done and hrHPV cases were identified. HPV 16/18 cases were further evaluated by colposcopy and biopsy.

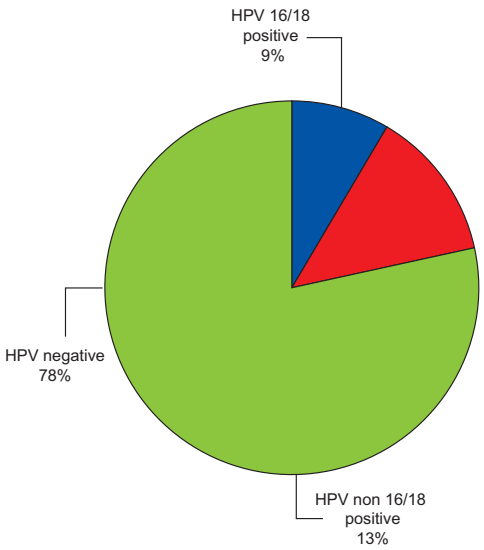

Figure 1: *HPV DNA status among the participants*

Results

More than three-fourths (n=120) of the patients were HPV DNA negative. Only 13 (9%) patients were HPV DNA 16/18 positives while 20 patients (13%) were HPV DNA non 16/18 positive (Fig. 1).

Table 1: High risk HPV +ve cases among different age

Age (n=153)	HPV – ve (120, 78.4%)	HPV + ve (33, 21.6%)	16/18+ve (13, 8.5%)	Non 16/18+ve (20, 13.1%)
25-29 (26, 16.9%)	23	3	1	2
30-34 (26, 16.9%)	21	5	3	2
35-39 (34, 22.2%)	30	4	1	3
40-44 (24, 15.7%)	18	6	4	2
45-49 (22, 14.4%)	15	7	3	4
>50 (21, 13.7%)	13	8	1	7

Distribution of high-risk HPV +ve cases among different age is presented in Table 1. Most of the patients (n=4) of HPV 16/18+ve were from 40-44 years age group while most of the respondents (n=7) of HPV non 16/18 +ve were from more than 50 years age group.

Table 2: Cross tabulation between age group and HPV DNA status among participants

Age in years	HPV DNA 16/18 positive	HPV DNA non 16/18 positive	*p*-value
Below 40	5	8	1.00
Above 40	8	12	

Five patients below 40 years of age were tested positive for HPV DNA 16/18 while 8 patients were tested positive for HPV DNA non 16/18. In above 40 years age these numbers were eight and 12 respectively. However, this difference was statistically not significant (χ^2=0.008, df=1; *p*=1.00) (Table 2).

Table 3: Histopathological findings of HPV 16/18 positive cases

No. of HPV 16/18 +ve cases	Normal	CIN1	CIN-2	CIN3
(13, 9%)	04 (31%)	07 (54%)	02 (15%)	0 (0.0)

Colposcopical findings correlated with the histopathological report of HPV 16/18 positive cases are shown in the Table 3. Out of 13 HPV 16/18 positive cases CIN 1 was found in 7 cases and CIN 2 in 2 subjects. Four patients were found normal on colposcopy. All positive cases were available for follow up.

Discussion

HPV DNA test has been shown to be more effective than commonly used screening methods for detecting and preventing cervical cancer. The recently published "WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention" recommends the use of such DNA-based HPV testing as a first-choice screening method.[5]

The prevalence of HPV virus infection varies from7-14% among the general population of South Asia, mainly in India, Bangladesh, Sri Lanka and Nepal.[6] In the current study, HPV positive cases were 21.6%, among them 16/18 positive cases were only 8.5%. These findings are consistent with that of the Sultana et al. study.[7] In context of their study, they reported the most prevalent high-risk HPV types, in order of prevalence rate, were HPV16, HPV18, HPV58, HPV45, HPV31 and HPV33. Both HPV 16 and HPV 18 were present in 21% of the cases.

Study conducted at BSMMU (the national screening Centre from 2005-2020, among 30,482 VIA positive referred case for colposcopy), only 16% were positive for high grade lesions and malignancy, 49% (14,856) were normal.[8] More than 80% of cases were

colposcopically normal. In the current study 78% cases were HPV negative. Colposcopical examination was done only in 8.49% (13), who were HPV 16/18 positive. Among them only 15% (2) were high grade lesions, selected for treatment and follow-up. Low grade lesions and normal histopathology were 85% (11). A Dutch cervical cancer screening program, a modeling study done to reduce unnecessary referral to colposcopy clinic published on 2021. The study recommended hrHPV test to avoid colposcopical burden. Therefore, reduction of unnecessary referral to colposcopy in hrHPV positive women is best achieved by using HPV 16/18 genotype.[9]

Conclusion

CC screening by hrHPV DNA test identifies women who currently have high grade cervical lesion who are in greater risk of developing the invasive disease in future. Low- and middle-income countries need to consider hrHPV test as primary screening test to reduce false positive results from VIA, without producing false negative report.

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Original Article

Cancer J Bangladesh 2021;2(2): 11-15
http://nicrh.gov.bd/publication

Performing Chi-square Test in Cancer Research by Using Excel

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Citation: Islam MJ. Performing Chi-square Test in Cancer Research by using Excel. Cancer J Bangladesh 2021;2(2):11-15.

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Received : 09 June 2021
Accepted : 28 August 2021
Published : 08 November 2021

Abstract:

In cancer research, various categorical variables are dealt with that can be summarized as a series of counts. These counts are usually arranged in a contingency table. The chi-square test of independence can be used to evaluate whether there is an association between the rows and columns in a contingency table. In other words, this statistic can be used to determine whether there is any difference between the study groups in the proportions of the risk factor of interest. The Chi-square test along with its logic of hypothesis testing was developed by Karl Pearson. The current article describes in detail how to calculate it easily by using the Excel program.

Key words: Categorical data analysis, Chi-square test, hypothesis testing, MS Excel

Introduction:

Pearson's Chi square test is the most substantial contribution to the theory of statistics invented by Karl Pearson in 1900.[1]

The most fascinating feature of Chi square distribution was that, one could use the statistical methods that did not depend on the normal distribution to interpret the findings.[2] Chi square test is a nonparametric test used for two specific purposes: (a) To test the hypothesis of no association between two or more groups (i.e. to check independence between two variables); (b) and to test how likely the observed distribution of data fits with the distribution that is expected (i.e., to test the goodness of fit). It is used to analyse categorical data (e.g., smokers and non-smokers, Argentina and Brazil fan etc.), it is not meant to analyse parametric or continuous data (e.g., height in cm, weight in kg etc.). But if we can convert the continuous data into categorical data Chi-square (χ^2) test can be applied.

Assumptions underlying a Chi square test

There are three prerequisites to be full-filled before a chi-square test can be done. 1. The data should be randomly drawn from a population. 2. The expected value of any cell should not be less than five. 3. If value in any cell is less than five it should not occupy more than 20% of cells, i.e., in 2X2 table no cell should contain an expected value less than five. Violation of this assumption need to be corrected by Yate's correction or Fisher's Exact test (mostly used).[2]

The formula to calculate a Chi square statistics

The formula[3] for calculating a Chi-square statistic is:

$$\chi = \sigma^{n}_{=1} \frac{(O - E)^2}{E}$$

Where,

O = observed frequency,

E = expected frequency.

Firstly, expected count is deducted from the observed value to find the difference between the two. Then the square of the difference is calculated so that the negative values can be omitted. In next step, the square of the difference is divided by the expected count. The sigma sign in front of them means that one has to sum up these values calculated for each cell. As for example, suppose a researcher wants to find out that whether there is an association between smoking and lung cancer.

The null and alternative hypothesis will be:

H_0: There is no association between smoking and lung cancer.

H_a: There is an association between smoking and lung cancer.

The basic step for calculating a Chi-square test is setting up a 2 × 2 contingency table (Table 1).

Table 1: General notation for a 2×2 contingency table

Lung cancer	Smokers	Non-smokers	Total
Yes	a	b	a+b
No	c	d	c+d
Total	a+c	b+d	a+b+c+d=n

Chi-square test can be done manually but it is cumbersome. Different statistical software like SPSS for Windows can be used to calculate Chi-square test easily. But it can also be performed with MS Excel. In this article we will learn how to do this in MS Excel.

Let's extend the previous example. Suppose we randomly recruited 500 respondents in that study. The following table shows the results of the study:

Table II: Occurrence of lung cancer in smokers and non-smokers

	A	B	C	D
1	**Lung cancer**	**Smokers**	**Non-smokers**	**Total**
2	Yes	21	9	30
3	No	219	251	470
4	Total	240	260	500
5	**Observd valeus**			

Let us perform the following steps to conduct a Chi-Square test of independence to determine whether smoking is associated with development of lung cancer or not.[4]

Step 1: Define the hypotheses.

Chi-Square test of independence will be performed by using the following hypotheses:

- **H_0:** Smoking and development of lung cancer are independent.
- **H_a:** Smoking and development of lung cancer are *not* independent.

Step 2: Calculate the expected values.

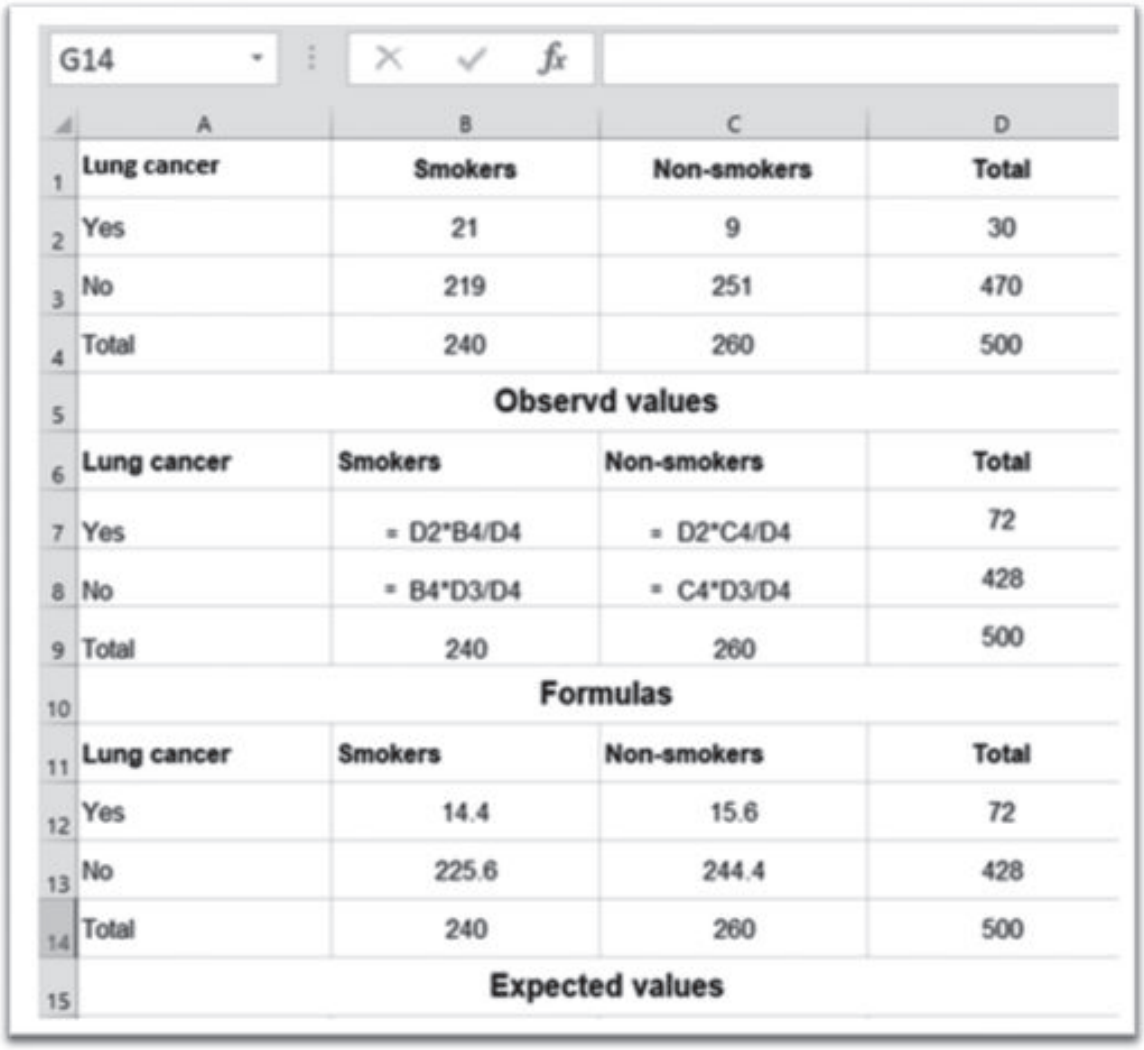
Now it is time to calculate the expected values for each cell in the contingency table using the following formula:

$$Expected\ value\ \frac{(Row\ sum\ \ Column\ sum}{Table\ sum}$$

For example, the expected value for smokers who developed lung cancer: (30*240) / 500 = 14.4.

We can repeat this formula to obtain the expected value for each cell in the table:

Table 3: Calculation of expected values from the given formula



	A	B	C	D
1	**Lung cancer**	**Smokers**	**Non-smokers**	**Total**
2	Yes	21	9	30
3	No	219	251	470
4	Total	240	260	500
5		**Observd values**		
6	**Lung cancer**	**Smokers**	**Non-smokers**	**Total**
7	Yes	= D2*B4/D4	= D2*C4/D4	72
8	No	= B4*D3/D4	= C4*D3/D4	428
9	Total	240	260	500
10		**Formulas**		
11	**Lung cancer**	**Smokers**	**Non-smokers**	**Total**
12	Yes	14.4	15.6	72
13	No	225.6	244.4	428
14	Total	240	260	500
15		**Expected values**		

Step 3: Calculate $(O-E)^2$ / E for each cell in the table.

Next, we will calculate **$(O-E)^2$ / E** for each cell in the table where:

- **O:** observed value
- **E:** expected value

For example, smokers would have a value of: $(21-14.4)^2/14.4=$ **3.025**

We can repeat this formula for each cell in the table:

Table 4: Calculation of $(O-E)^2/E$ values

H25

	A	B	C	D
1	Lung cancer	**Smokers**	**Non-smokers**	**Total**
2	Yes	21	9	30
3	No	219	251	470
4	Total	240	260	500
5	**Observd values**			
6	Lung cancer	Smokers	Non-smokers	Total
7	Yes	= D2*B4/D4	= D2*C4/D4	72
8	No	= B4*D3/D4	= C4*D3/D4	428
9	Total	240	260	500
10	**Formulas**			
11	Lung cancer	**Smokers**	**Non-smokers**	**Total**
12	Yes	14.4	15.6	72
13	No	225.6	244.4	428
14	Total			500
15	**Expected values**			
16	Lung cancer	**Smokers**	**Non-smokers**	**Total**
17	Yes	= (B2-B12)^2/B12	= (C2-C12)^2/C12	72
18	No	= (B3-B13)^2/B13	= (C3-C13)^2/C13	428
19	Total	240	260	500
20	**Formulas**			
21	Lung cancer	**Smokers**	**Non-smokers**	**Total**
22	Yes	3.025	2.792307692	72
23	No	0.193085106	0.178232406	428
24	Total	240	260	500
25	**(O-E)^2/E values**			

Step 4: Calculate the test statistic χ^2 and the corresponding p-value.

The test statistic χ^2 is simply the sum of the values in the last table.

The p-value that corresponds to the test statistic χ^2 can be found by using the following formula:

=CHISQ.DIST.RT(x, deg_freedom)

where:

- **x:** test statistic χ^2
- **deg_freedom:** degrees of freedom, calculated as (number or rows-1) * (number of columns-1)

The test statistic χ^2 turns out to be **6.189** and the corresponding p-value is **0.013**.

Table V: Calculation of test statistics value and *p*-value

Test statistics	=	Sum(G12:H13)
p -value	=	CHISQ.DIST.RT(x, deg_freedom)

Test statistics	6.189
p -value	0.013

Step 5: Drawing conclusion.

Since this p-value is less than 0.05, we can reject the null hypothesis. This means we do have sufficient evidence to state that there is an association between smoking and development of lung cancer.

Conclusion:

Pearson's Chi square test is the most widely used test by medical professionals. With different statistical software this test can be done with great accuracy. But not all are acquainted with such software. In that case very familiar Excel program, which is invariably present in every researcher's laptop, can be used with great ease.

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Original Article

Cancer J Bangladesh 2021;2(2): 16-21
http://nicrh.gov.bd/publication

Clinicopathologic Features and Factors Related to Late Presentation of Oral Squamous Cell Carcinoma

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Citation: Haque A, Khandker MNH, Siddika A, Ali SMM, Afroze YJ, Baidya P, Sunny NAH, Hasan MN Clinicopathologic Features and Factors related to Late Presentation of Oral Squamous Cell Carcinoma. Cancer J Bangladesh 2021;2(2): 16-21.

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Received : 26 September 2021
Accepted : 17 October 2021
Published : 08 November 2021

Abstract

Background: *The incidence rate of lip & oral cavity cancer in Bangladesh is about nine percent and it is the 3rd and 5th most frequent cancer for men & women respectively. The aim of this study was to determine the clinicopathologic features and factors for diagnostic delays.* ***Materials and Methods:*** *This cross-sectional study was carried out in the National Institute of Cancer Research and Hospital (NICRH) on 84 biopsy proven advanced stage (TNM stage III or IV) oral squamous cell carcinoma patients.* ***Results:*** *Mean age of the patients was 53 ± 11.2 years with female predominance (55%). Two-thirds of the patients had no education and the same percentage of patients came from a lower socio-economic group. Nearly 90% of patients were habituated with betel quid with smokeless tobacco and 32% patients had history of smoking. According to clinical stage of lesion, stage III, IVA & IVB lesions were 15%, 66% and 19% respectively. Fifty one percent lesions involved more than one subsite of the oral cavity. More than 50% patients sought treatment within two months of appearing the symptom and 12% of patients delayed more than 6 months. Registered dentists and physicians were consulted initially by 6% and 25% of patients respectively. Eighty four percent patients had no knowledge about oral cancer. Factors for delayed presentation include lack of knowledge (80%), economic crisis (57%), lack of treatment knowledge (45%), inadequate support from family (32%) and communication problem (21%). More than 50% of patients identified lack of knowledge about cancer as the main reason followed by economic crisis for 25% of patients for late presentation.* ***Conclusion:*** *Educational interventions on the population should be prioritized to increase awareness about the symptoms and consequences of oral cancer so that it can be diagnosed at the initial stage.*

Key words: *Oral squamous cell carcinoma, treatment delay*

Introduction:

Cancer is the leading cause of death in developed countries and is the 2nd leading cause of death in developing countries.[1] According to Globocan 2020 prediction 19.3 million new cases and 10 million cancer deaths were estimated to occur in 2020 worldwide.[2] The incidence rate of different types of cancer varies widely depending on geography, dietary habits, socioeconomic conditions & lifestyles. According to the International Association of Cancer Registries, the greatest burden of oral cancer in the world is in South Asian Countries. The incidence rate of lip & oral cavity cancer in 2020 in Bangladesh was 8.9% and it was the 3rd and 5th most frequent cancer for men & women respectively.[2] One study conducted in Dhaka Dental College in 2012 showed that 22% of admitted patients suffered from oral cancer.[3] Although the primary risk factor for oral cancer is the tobacco, areca nut chewing is also responsible for a significant portion of the global burden of oral cancer.[4] Tobacco in the form of smoking and smokeless tobacco in the form of betel quid, gul, khaini, zarda, gutkha etc. are commonly used in South Asian countries such as India, Pakistan, Bangladesh and Sri Lanka. Different studies have demonstrated the association between smokeless tobacco and oral cancer.[5]

Around 50% patients with oral cancer present with advanced-stage disease.[6] The proportion of patients presenting with late-stage disease has not reduced in the past four decades.[7] Forty percent of cases present with regional metastases and 6% with distant metastases at the moment of diagnosis, despite the examination of oral cavity does not require any special instrument.[8] Late presentation of oral cancer requires more radical treatment which leads to poor prognosis. It is also associated with additional treatment burden and worse health related quality of life outcomes.

These findings have led to the investigations for the causes of these significant diagnostic and therapeutic delays. Various studies have assessed the determinants for diagnostic delay for oral cancer. A systematic review conducted by Scott et el. found that a significant proportion of patients delay to visit a health care provider after self-identification of an ulcer in the oral cavity.[9] Patients usually report to the doctor only when there is pain or the ulcer interferes with eating or speaking.[8] Most of the data highlighting the factors for patients delay are attributable to studies in the western literature.[10] There is extreme scarcity of literature pertaining to our population about this issue.[11] As because there is a significant difference in the socio-economic profile and cultural patterns between our population and western population, the available data cannot be interpreted onto our population. The aim of the present study was to determine the clinicopathologic features and factors for diagnostic delays in oral cancer in our population.

Materials and Methods:

This cross-sectional study was carried out in the Faciomaxillary Surgical Oncology department of National Institute of Cancer Research and Hospital (NICRH) from January 2021 to June 2021. Eighty-four patients with biopsy proven advanced stage (TNM stage III or IV) squamous cell carcinoma of oral cavity were included in the study. Early stage (TNM stage I or II) cancer and patients unwilling to comply were excluded from the study. A structured questionnaire was utilized to record information related to the study. The variables considered included age, sex, education level, occupation, habits (smoking, betel-quid chewing and alcohol), site of lesion, TNM stage, duration of symptom, knowledge about oral cancer and causes of delay. The statistical analysis was carried out using the SPSS for Windows (IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) software.

Results:

A total of 84 patients (mean age 53 ± 11.2) with female predominance (55%), entered the study. More than 30% patients were below 45 years of age. Two-thirds of the patients had no education and there was no patient who completed a graduation level of study. Among the patients, 16 (20%) were retired from work and 31(40%) were housewife- both these groups were dependent on their family members for the treatment. Two-third of the patients came from a lower socio-economic group and no patient entered from the upper strata of the society. Regarding history of habit, nearly 90% of patients were habituated with betel quid with smokeless tobacco, where as 32% patients had history of smoking (Table 1).

Table-1: Characteristics of participant

Variable	Frequency	Percentage
Gender		
Male	38	45
Female	46	55
Age group distribution (yrs.)		
<35	5	6
36-45	22	26.2
46-55	26	31
56-65	21	25
>66	10	11.9
mean (±SD)	53.10±11.17	
Education		
No education	56	66.6
Primary	14	16.7
Secondary	14	16.7
Occupation		
None	16	19
Service	4	4.8
Business	9	10.7
Housewife	31	36.9
Farmer	16	19
Day labor	4	4.8
Others	4	4.8
Social standing		
Middle class	29	34.5
Lower class	55	65.5
Position in family		
Earning member	37	44
Dependent on other	47	56
Habits		
Betel quid with smokeless tobacco	75	89.3
Betel quid without smokeless tobacco	5	6
Smoking	27	32
Alcohol	2	2.4

More than half of the patients presented to us with a lesion that involved more than one subsite of the oral cavity (Fig. 1). Buccal mucosa (22%) was the next predominant site followed by retromolar trigone (6%), palate (6%), lip, lower vestibule and lower gingiva with equal distribution (3.6%). According to clinical stage of lesion, stage III, IVA & IVB lesions were 15%, 66% and 19% respectively (Fig. 2). There was no early-stage cancer because these lesions were not included in this study.

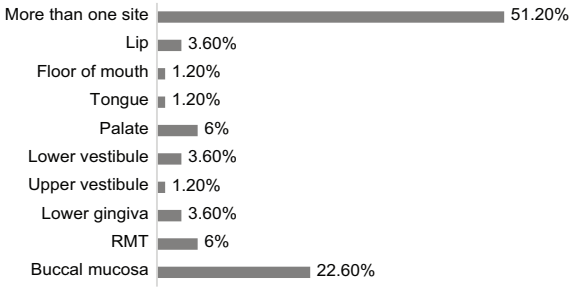

Fig.-1: Site of involvement of oral cancer

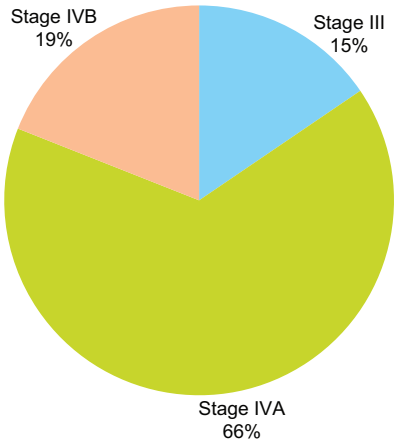

Fig.-2: *Distribution of TNM stage of oral cancer*

Table II illustrates that more than 50% patients sought treatment within two months of appearing the symptom. Twelve percent of patients delayed more than 6 months until the lesion increased in a considerable size. Rural medical practitioners were chosen as the first attending physicians by 40% patients and registered dentists and physicians were consulted initially by 6% and 25% of patients respectively.

Table II: Time and Type of First Attending Physician

Parameter	Number	Percentage
Time elapsed to start first treatment after appearing of symptom:		
0-2 months	43	51
3-4 months	26	31
5-6 months	5	6.0
>6 months	10	12
First attending physician:		
Rural medical practitioner	34	40.5
Local pharmacy	11	13.1
Homeopathy	10	11.9
Kabiraj	3	3.6
Registered physician (BDS)	5	6.0
Registered physician (MBBS)	21	25.0

According to the current study, 84% patients had no knowledge about cancer, 12% had inadequate knowledge and only 4% patients had adequate knowledge about cancer. Sixty six percent of patient's attendant had no knowledge about oral cancer (Table III).

Table III: Knowledge about cancer

Knowledge	Number	Percentage
Patient's knowledge		
No knowledge	71	84.5
Inadequate knowledge	10	11.9
Adequate knowledge	3	3.6
Attendant's knowledge		
No knowledge	56	66.7
Inadequate knowledge	21	25
Adequate knowledge	7	8.3

Among the factors responsible for delaying to seek treatment, 80% patients stated that lack of knowledge about cancer was one of the reasons. The next contributing factor was economic crisis (5.7%), followed by lack of knowledge about treatment (45%), lack of support from the family (32%), communication problem (21%), various social myth about cancer (17%). When patients and their attendants were asked to identify the main reason for the treatment of cancer, 57% of patients noticed that lack of knowledge about cancer was the main reason and one-fourth of patients identified economic crisis as the main contributing factor (Fig. 3).

Table IV : *Factors of Delay*

Factors	Number	Percentages
Economic crisis	48	57.1
Lack of knowledge	67	79.8
Lack of treatment knowledge	38	45.2
Communication problem	18	21.4
Social Myth	15	17.9
Wrong direction	15	17.9
Lack of support from family	27	32.1

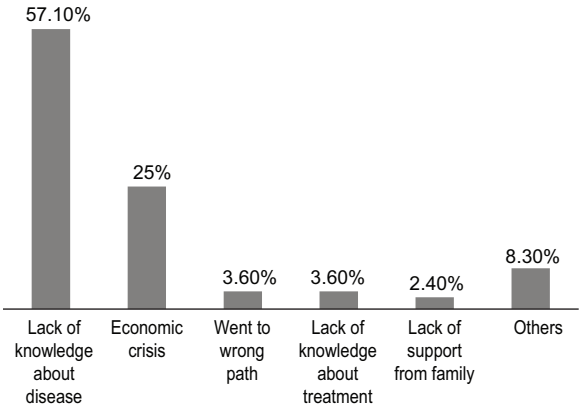

Fig.--3: *Main cause of delay according to patient's opinion*

Discussion:

NICRH is the only dedicated government hospital in the country for treatment of cancer patients having all 3 modalities of treatment: surgery, chemotherapy and radiotherapy. In a previous study carried out in the faciomaxillary surgical oncology department [12], it was found that two-thirds of patients present with advanced stage of the disease- some are very ugly-looking with huge loss or necrosis of cheek. It was then decided to include only stage III & IV diseases in the current study to identify the reasons behind delayed presentation of these patients.

Mean age of the patients was 53 years which is higher to a study carried out in Pakistan but 7 years lower to a study conducted in South India.[13,14] In the Indian study, nearly 80% patients were more than 50 years old but, in the present study, nearly one-third of patients were below 45 years. This finding suggest that more young people are being diagnosed with oral cancer. Fifty-five percent of the patients were female which are similar to the studies conducted in India and Turkey.[11, 15] Two-thirds of the patients had no education at all and there was no patient who completed the graduate level of study. A population-based study in South-India found that low educational status is associated with advanced stage cancer of oral cavity which correlates to the current study findings.[14] Education level is associated with cognitive function and health consciousness which affect health-seeking behaviors.

Dependency on others for treatment is strong barrier for early treatment of diseases. More than fifty percent (House-wife 37% and no-occupation 19%) of the

patients were dependent on the other family members for financial support of their treatment. There was no patient from the upper-class society in the present study. Either they do not come to the Government hospital or they receive treatment at an early stage of the disease.

Chewing habit of betel quid and other hazardous substances have a regional variation with as high as 22% in Southeast Asia and <1% in the Western Pacific Region.[16] Ninety percent of the patients were habituated with chewing tobacco which is much higher (77%) than a similar study in Pakistan.[13] Studies on our population also confirmed that over half of the habitual chewers have no proper education and it is more prevalent in rural areas.[17, 18]

As because the advanced stage cases were only included in the present study, we got many patients who had involvement of more than one subsite of the oral cavity which does not correlate to any other study. Initially the lesions started in a single site of the oral cavity but gradually involved multiple sites due to delaying of seeking treatment. There were some unfortunate patients with huge skin involvement and necrosis of tissue – very difficult to imagine how they stayed so many days with these types of lesions. Regarding the rest of the lesions, buccal mucosa was the most predominant site (22%). Although tongue is the most common site for oral cancer in the western literature, buccal mucosa is the commonest site for oral cancer in the South-Asian countries.[10] This is mainly due to the habit of excessive chewing tobacco and keeping these substances in the vestibule for a long time.

Mandal et al. conducted a study at a regional cancer institute in Eastern India and found that only 7% patients reported in the institute within 2 months of noticing the symptom and nearly half of the patients reported after 6 months of onset of symptoms.[19] This is contradictory to our finding where half of the patients sought for a treatment within 2 months of initiation of disease. First attending physician plays a key role for the subsequent management of a disease. We found in our study that only 6% and 25% patients consulted with a registered dentist and physician respectively, rather 40% of them went to the rural medical practitioner first. In a recent study in Poland, Rutkowska et al. found that 35% of patients attended to their general practitioner first followed by 31% to the dentist.[8] Another similar type of study conducted in India observed that patients with late stage diseases sought consultation with unqualified practitioner, Ayurveda and Homeopathy more frequently than early stage diseases.[10] None of our patients identified visible benefit of these kind of treatment but transformed the early stage disease to a late stage lesion. Although it is widely accepted that oral cancer is best identified by a dentist or a maxillofacial surgeon than other specialists, only a few of the patients reported to a dentist at their initial visit.[7]

The most striking finding of this study is that 84% of our patients and two-thirds of their attendants had no knowledge about cancer. Scott et al. conducted a study on patients with potentially malignant disorder and concluded that patients knowledge of oral cancer, severity of life events in the patient's delay period, and ability to seek help from others were independent predictors of patient delay.[20] In a similar type of study in 2014, Panzarella et al. found that unawareness, personal experience of cancer, denial, knowledge of cancer were important predictor for patient delay.[21] Our study revealed that 57% of the patients delayed to consult with a physician due to financial crisis. Public health insurance system does not exist in our country and it is not possible for the poor people to bear the expenses of the treatment. This factor also pushes the patients move to other cheaper means of treatment methods like Homeopathy, Ayurveda etc. which in turn deteriorates the condition. "What was the main reason for delaying treatment?"- when this question was asked to the patients and their attendants, most of them answered that they had no knowledge about the symptoms of cancer and if they knew that it would be diagnosed as cancer in future, they would receive the treatment at any cost at the initial stage of the disease.

The current study had some limitations. It was a single center study with a small sample size of the advanced stage of oral cancer cases only. Inclusion of both early and late-stage diseases in the study is necessary to identify the association of various predisposing factors for late-stage diagnosis.

Conclusion:

It is evident from the present study that lack of proper knowledge about oral cancer is the main contributing factor for patient delay in our hospital. Educational interventions on the population should be prioritized to

increase awareness about the symptoms and consequences of oral cancer so that it can be diagnosed at the initial stage. Early-stage disease requires less invasive surgery which is associated with good quality of life and high overall survival. Conversely, the results of late diagnoses are negative patient outcomes with respect to both morbidity and mortality.

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Case Report

Cancer J Bangladesh 2021;2(2): 22-27
http://nicrh.gov.bd/publication

Final Diagnosis - A 38-Year-Old Man with Epithelioid Sarcoma

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Citation: Bhuiyan AKMMU, Alam MS, Arjuman F. Final Diagnosis - A 38-Year-Old Man with Epithelioid Sarcoma. Cancer J Bangladesh 2021;2(2): 22-27.

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Received : 25 August 2021
Accepted : 15 September 2021
Published : 08 November 2021

Abstract

Epithelioid sarcoma (ES) is a relatively rare high-grade soft tissue sarcoma of unknown histogenesis. Due to its insipid presentation, infrequent occurrence and histologic resemblance with other benign & malignant diseases diagnosis of ES is considerably difficult. Taking the advent of immunohistochemistry for confirmation of diagnosis is warranted. A case is presented here that highlights the difficulties that had been mentioned earlier to reach the final diagnosis of ES.

Keywords: *Epithelioid sarcoma, Immunohistochemistry*

Introduction

Epithelioid sarcoma (ES) is a distinct clinicopathologic entity. This tumor appears relatively rare soft tissue tumor of unknown histogenesis. It is usually a slow-growing tumor and mostly occurs within the distal extremities of young adults. Both local recurrence and metastasis are common. An aggressive subtype of ES has been identified known as 'proximal-type/axial-type' predominantly develops in pelvis, perineum & genital tract.[1] The tumors in these cases is deep seated & tends to occurs in older patients.[2] Commonly, the tumor presents as a slow-growing, painless, and firm nodule that may become ulcerated. The benign clinical presentation and low occurrence rate make diagnosis of the lesion difficult during the first stages, as these symptoms are often confused with other diseases with similar presentations. The similarities between the histologic presentation of epithelioid sarcoma and other benign and malignant diseases make diagnosis challenging, but advances in immunohistochemistry have facilitated the process and increased the frequency of proper diagnosis.[3] The tumor cells are most often

immunoreactive to cytokeratin antibodies AE1/AE3, epithelial membrane antigen (EMA), and vimentin. This high-grade sarcoma is reported to possess an area local recurrence rate as high as 77% and a metastatic rate of up to 45%. The standard treatment of epithelioid sarcoma includes wide local excision followed by radiotherapy, with the option of multidrug chemotherapy, although there has been no published study indicating the benefits of adjuvant chemotherapy.[3] Herein, we present a case report of epithelioid sarcoma of the lower extremity with recurrent lesion & nodal metastasis, emphasizing the difficulty that may be encountered in arriving at the correct diagnosis.

Case History

A 38 years old patient admitted on October, 2012 in the Dept. of Surgical Oncology of NICRH with the complaints of (i) recurrent and rapidly progressing soft tissue swelling in his left thigh for 4 /5 months and (ii) development of recurrent multiple nodular lesions in left leg and foot for the same duration. His annoying sufferings actually started 6 years back when he had to undergo "wide excision" for a 6x4 inches, mobile soft ovoid lesion in dorso-medial aspect of left foot in April 2006 in SSMCH. Preoperative FNAC revealed oval and spindle shaped cells in tissue debris with no malignancy seen. Post- operative HPR was Chondromyxoid Fibroma. For his recurrent lesion in the same area mostly in left sole with X-ray Lt. foot showing soft tissue mass without bony involvement (Fig. 1), he again underwent wide local excision & skin grafting on July 2007 in a clinic. HPR revealed nodular hydradenoma with no malignancy. After a short gap of 3 years, he developed a fungating proliferative mass approx. 10x7x6 cm in mid left foot. This time he went abroad and treated with "wide excision with sural arterial flap coverage" in the dept. of orthopaedics in CMH, Vellore, Channi, India on 13th Jan. 2010. HPR revealed "Low grade Sarcoma with ossification left foot. Skin margins free but deep soft tissue margin involved by tumor." He got RT 6600 cGy in 33# which was completed on 26th April 2010. After a very short eventless period on his follow up in March 2011 PET – CT showed "multiple enlarged nodes in left leg and inguinal region. But no significant lesion in left foot or other parts of body was found. But for his multiple new nodular lesions, in April 2011, "wide excisions from anteromedial & posterior calf lesion, medial malleolar lesion & Lt Inguinal lymphadenectomy" were done in same hospital. That time HPR impressions was "Recurrent Intermediate grade sarcoma with 1 of 4 inguinal LN deposit." He then completed 6 cycle Chemotherapy with Doxorubicin & Ifosfamide on 24th August 2011 planned by CMH, Vellore. Few months later in April 2012 he was again operated in BSMMU for rapidly developing soft tissue mass in upper thigh and multiple soft tissue lesions left leg. HPR (3/5/12) revealed "High grade sarcoma, suggestive of Synovial Sarcoma." Review of the slide in NICRH (Nov, 2012) revealed Epithelioid sarcoma. Afterwards he attended in NICRH for his rapidly developing growth within weeks after operation at BSSMU in the same sites.

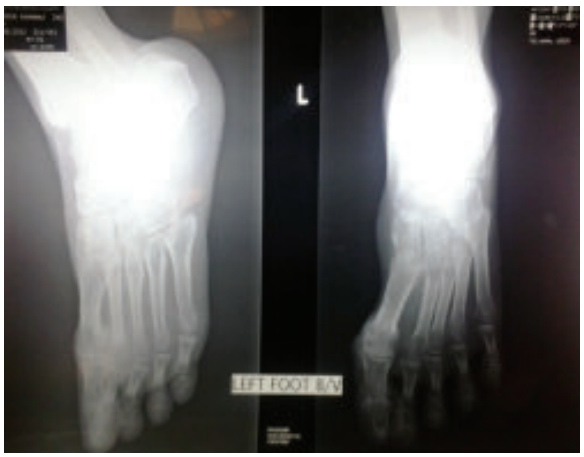


Fig.-1: *X-Ray Lt. foot*

In the department of Surgical Oncology, general & local examination revealed no abnormalities in all other system except left lower limb. An irregular shaped, 7x6 inch, nontender multilobulated partially mobile mass was present in the superomedial aspect of left thigh. There were also multiple nodular lesions of similar characteristics present in leg and great toe in previous scar. MRI (Fig. 2) showed significant recurrent lesions. CXR (Fig. 3) and USG of abdomen were normal.

On treatment, after proper counselling and preoperative anaesthetic checkup. Disarticulation of left hip was done on 17th October, 2012. Final HPR revealed suggestive of synovial sarcoma.

Fig.-2: *MRI (T1 & T2 weighted image)*

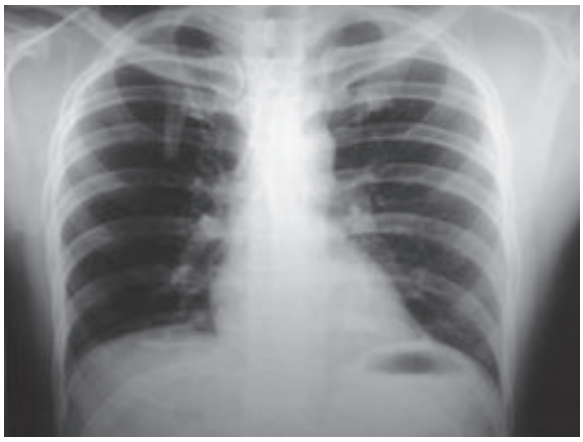


Fig.-3: *CXR*

As the initial HPR reports were confusing we personally contacted with our renowned histopathologist and he took the matter seriously. He reviewed the case & slides with considerable time and finally came to a conclusion that it was a case of "Epithelioid Sarcoma" (Fig. 4). Immunohistochemistry of the specimen revealed cytokeratin AE1/AE3 (+ve), EMA (+ve) & vimentin (+ve) that confirmed the diagnosis of Epithelioid Sarcoma (Fig. 5). The patient was on usual follow up schedule in our institute for 5 years that is up to 2018. Fortunately, he developed no recurrence in that period. Now the patient is on yearly follow up schedule.

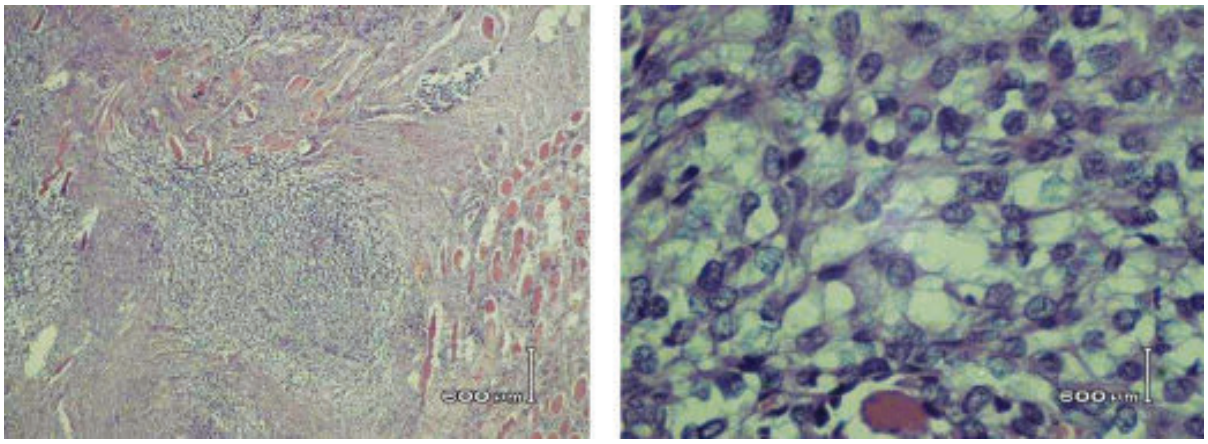
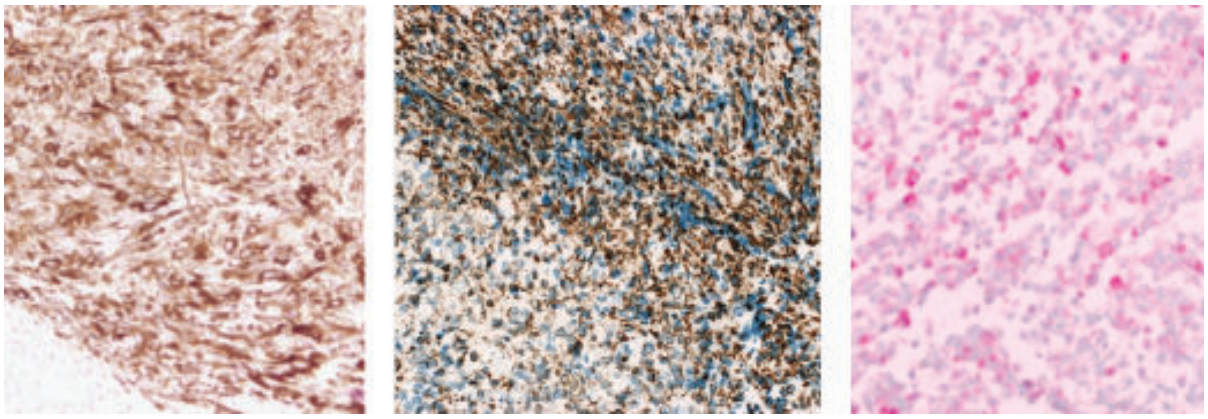


Fig.-4: *Histopathological slide of specimen (Epithelioid Sarcoma).*



Cytokeratin (+ve) Vimentin (+ve) EMA (+ve)

Figure – 5: *Immunohistochemistry (IHC) of specimen*

Discussion

Epithelioid sarcoma could also be a rare high-grade sarcoma with an annual overall incidence of 0.041 per 100,000 persons. Frequently, the tumor arises within the distal upper extremity (47%), typically within the hands and the forearms of people between the ages of 10 and 35 years. Other commonly affected sites include the distal lower extremities (15%), proximal lower extremities (12%), & proximal upper extremities (10%). The distal lower extremity is the second most common primary site of epithelioid sarcoma, as per reports by Enzinger and Chase.[3] Chase and Enzinger reported the recurrence and metastasis rates to be 77% and 45%, respectively, with the foremost frequent sites of metastasis being lung (51%), lymph nodes (34%), and scalp (22%). Other sites of spread included bone (13%), brain (13%), and liver (12%). Unlike the bulk soft tissue sarcomas, epithelioid sarcoma displays an unusual tendency to spread through the lymphatic and vascular system, thus explaining its ability to spread to areas such as the lymph nodes and therefore the bone marrow, also because the lungs and therefore the brain. Misdiagnosis of epithelioid sarcoma is fairly common owing to its insipid presentation and infrequent occurrence.

Our patient presented with 4/5 months of several times recurrent soft tissue mass in multiple sites of left lower limb underwent 5 times operation in home & abroad. Initial assessment and radiographic findings at the outside of this institution led to a diagnosis of multiple benign lesions. Enzinger and colleagues report 148 cases of incorrect initial diagnosis of epithelioid sarcoma.[3] The tumor was often confused with numerous other

benign conditions, such as fibrous histiocytomas, fasciitis, reactive processes, synoviomas, and fibromas. In addition to the benign clinical presentation and infrequent occurrence, the uncommon primary location of the tumor prevents epithelioid sarcoma from being considered as a possible diagnosis. The radiographic findings of epithelioid sarcoma are inconsistent, but a soft tissue mass with possible speckled calcifications could also be demonstrated. Other infrequent findings include cortical thickening, cortical thinning, and localized demineralization. In our patient metaplastic ossification was found in the recurrent mass at foot after 3rd time operation. John et. al. shows positive findings are often followed by MRI in order to further assess the abnormalities. They performed F-18 FDG PET-CT of the patient to identify multiple lytic lesions in the left lower distal extremity, demonstrating both local invasion and distant metastasis. Incisional biopsy was performed on the most proximal lesion of the left proximal tibia confirmed the diagnosis of epithelioid sarcoma.[3] A recent study published by Sakamoto and colleagues [4] discussed the potential usefulness of FDG-PET in epithelioid sarcoma.

The researchers presented a case during which a CT scan detected enlarged lymph nodes, but results from MRI and a plain radiograph were nonspecific and unable to spot any space occupying lesions. These imaging studies were followed by FDG-PET that showed multiple areas of increased uptake, which were confirmed at a later time to be epithelioid sarcoma. This study displays the worth of FDG-PET in assisting with early diagnosis and treatment of epithelioid sarcoma metastasis, a worth reiterated by this case.[3,4] In our particular patient multiple metastatic focus were identified in left inguinal LN on FDG PT-CT. It is interesting to notice the relatively high recurrence rate, as reported in earlier studies of epithelioid sarcoma following presumed wide excision of the tumor. PET for oncologic screening has been a reasonably recent advancement in medicine, with the first whole-body oncology image presented by Phelps and colleagues in 1991.[3] Microscopically, epithelioid sarcoma often demonstrates tumor cells that appear as highly eosinophilic epithelioid cells, which display a single or multi-nodular pattern with central necrosis; variants include ovoid or polygonal cells and plump spindle-shaped cells. The difficulty of executing a histological examination of epithelioid sarcoma lies in the disease's ability to mimic the appearance of other disease processes. Deep ulcerated lesions with large ovoid epithelioid cells could also be confused with poorly differentiated squamous cell carcinoma, while small superficial lesions with nodular patterns could also be mistaken for a benign inflammatory process. However, careful examination of the tumor cells will usually demonstrate a scarcity of intracellular bridges that are usually quite prominent in squamous cell carcinoma.

Furthermore, the use of immunohistochemical studies has been of tremendous assistance in correctly diagnosing epithelioid sarcoma. A recent study of 106 cases by Chbani and colleagues[5] demonstrated tumor cells staining positively for vimentin (100%), EMA (98%), cytokeratin AE1/AE3 (96%), andCD34 (62%). Surgical pathology reports from the other institution noted positive cytokeratin AE1/AE3 and vimentin staining but were negative for CAM5.2 and EMA.[3, 6] In accordance, we performed immunohistochemical confirmation of our specimen case. Our specimen revealed positivity for cytokeratin AE1/AE3, EMA & vimentin.

Epithelioid sarcomas seem to grow by way of the tendon sheaths and fascia during a proximal direction. Subsequently, dissemination occurs through the lymph vessels and/or the blood stream. Local recurrence is taken into account to be predictive of distant metastases and a significantly poorer survival. In a series by de Visscher et al.[4] patients developed local recurrence (50%) after a median follow-up of 4 months (range, 1–14 months); in the literature, this rate varied from 29% to 85%. Local recurrence mainly developed within 1 year after primary treatment. However, local recurrence can also occur after a few years.

Only one patient from the current study remained disease-free after resection of the local recurrence; the other 7 patients (87.5%) developed distant metastases after the local recurrence.[4] Our patient experienced 5 times recurrence within 6 year of time. The shortest time of recurrence was 6 months only. A central issue in local treatment, thus, is to realize an R0 resection.

Amputation does not cause to better survival than a successful local R0 resection. The advantage of an R0 resection also was emphasized during a series of patients with epithelioid sarcomas who were diagnosed

incorrectly. Local recurrence rates and deaths from the disease were increased as a result of an inadequately performed surgical resection.

When multiple local recurrences were present, local resection generally no longer was possible, and amputation of the affected extremity was the only remaining option.[4] We had to offer to our patient Hip disarticulation on this ground.

Conclusion

Rarity, bland presentation and mimicking nature of pathology makes epithelioid sarcoma diagnosis difficult and may lead to disease progression. The prognosis for patients with epithelioid sarcoma is poor, because a substantial number of patients present with extensive disease, lymph node metastases, and/or distant metastases. Undertaking a multidisciplinary approach is required to achieve proper diagnosis.

Acknowledgement

Prof. Md. Golam Mostofa, Ex-Head of Dept. of Histopathology, NICRH.

Disclaimer

There is no potential conflict of interest amid the authors.

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Case Report

Cancer J Bangladesh 2021;2(2): 28-30
http://nicrh.gov.bd/publication

Primary Leiomyosarcoma of Breast: A Case Report from Bangladesh

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Citation: Rahman MA, Alam S, Kabir S, Mallik MK, Saifullah K, Joarder EH. Primary Leiomyosarcoma of Breast: A Case Report from Bangladesh. Cancer J Bangladesh 2021;2(2): 28-30.

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Received : 12 August 2021
Accepted : 14 September 2021
Published : 08 November 2021

Abstract.

Background: *Primary leiomyosarcoma of the breast constitutes a histologic subtype that accounts for 5-10% of all breast sarcomas, making it an extremely rare diagnosis. Total number of reported cases in the literature is less than 70[4] to date. The first case goes back to 1968, and to our knowledge this is the 1st ever case report of primary leiomyosarcoma of breast in Bangladesh* ***Case report:*** *A 53-year-old perimenopausal female (G2P2) presented to the surgical oncology department with complaint of a lump in the left breast for three months. On examination, there was a 4 × 3 cm lump involving the upper outer quadrant of left breast which was firm in consistency with nodularity. FNAC showed morphologically it was a Phyllodes tumour but on core needle biopsy it revealed spindle cell lesion. IHC was done for further diagnosis and it showed features favoring low grade sarcoma favoring leiomyosarcoma as staining revealed a strong expression of vimentin and SMA while Epithelial Membrane antigen (EMA), S100 and CD34 were negative.* ***Conclusion:*** *Leiomyosarcoma is an extremely rare aggressive tumor with unfavorable prognosis.*

Keywords: *Primary leiomyosarcoma, breast, Bangladesh*

Introduction

Breast sarcomas are a rare type of malignant breast tumors that arise from the mesenchymal breast tissue, with an incidence of 0.5-1%.[1] Out of 27,881 patients diagnosed with breast malignancies at the Mayo Clinic, only 0.0006% were found to have breast sarcomas.[2] Primary leiomyosarcoma of the breast constitutes a histologic subtype that accounts for 5-10% of all breast sarcomas, making it an extremely rare diagnosis.[3] To date, the total number of reported cases in the literature is less than 70.[4] The first case goes back to 1968, and to our knowledge this is the 1st ever case report of primary leiomyosarcoma of breast in Bangladesh.

Case report

A 53-year-old perimenopausal female (G2P2) presented to the surgical oncology department with complaint of a lump in the left breast for the past 3 months. It was rapidly growing for the last one month with associated pain and heaviness according to the patient. She had no nipple discharge or any other significant complaints. Her appetite was normal with no significant weight loss, and there was no family history of similar illness.

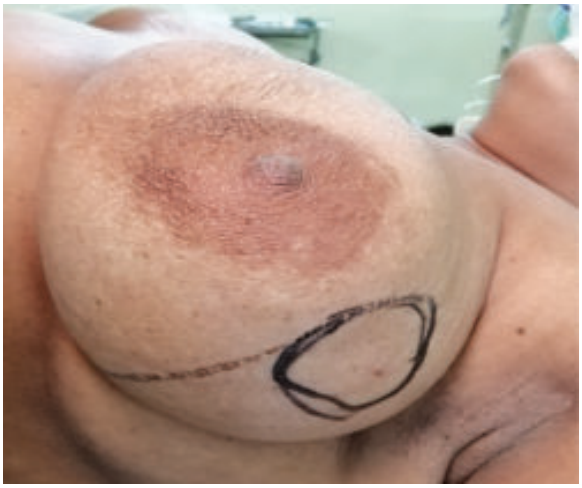

Fig. 1

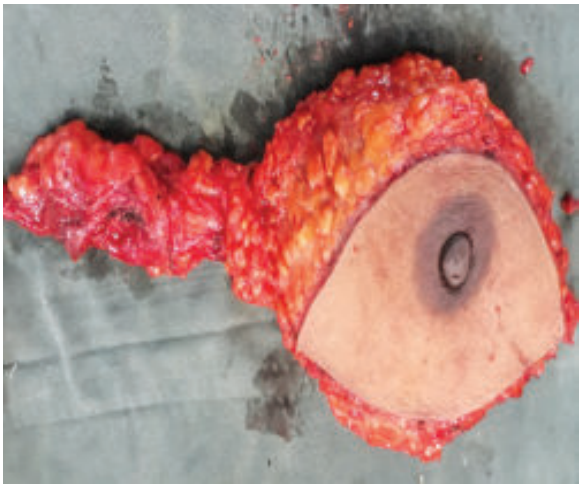

Fig. 2

On examination, there was a 4×3 cm lump involving the upper outer quadrant of left breast which was firm in consistency with nodularity. It was mobile and not fixed with the underlying structures or overlying skin. But the overlying skin was a bit tensed with no engorged veins. The lump seemed away from the nipple areolar complex which was not distorted (Fig.1). The axilla was normal and there were no enlarged lymph nodes. Examination of other systems were normal.

FNAC was done from the lesion that showed morphologically consistent with phyllodes tumor. Then for confirmation, core needle biopsy was taken. From the core biopsy specimen, Histopathology showed spindle cell lesion characterized by proliferation of stromal elements without glandular components with a mitotic count of 5/10 HPF. IHC was done for further diagnosis and it showed features favoring low grade sarcoma favoring leiomyosarcoma as staining revealed a strong expression of vimentin and SMA while epithelial membrane antigen (EMA), S100 and CD34 were negative. USG of breast showed irregularly marginate hypoechoic lesion in left breast with some axillary LNs, the largest of which has a diameter of <2 cm in size. Xray of chest and USG of abdomen was performed which did not reveal any metastases.

We performed a left sided modified radical mastectomy with axillary dissection up to level II axillary lymph nodes. Histopathology report confirmed the diagnosis of leiomyosarcoma which was not involving the underlying skeletal plane. The resected margins were free of tumor and cells expressed Vimentin, SMA and were negative for cytokeratin.

Discussion

Stromal sarcoma is the generic term given to malignant breast tumors that arise from the specialized stroma of this organ but which lack the epithelial component of phyllodes tumor. Histologically, most often these are ûbrosarcoma, but may also be leiomyosarcoma, liposarcoma, Primary sarcomas of the breast are rare and account for less than 1% of all breast neoplasms.[5] Among which most common histology is spindle cell sarcoma (13.4%), followed by leiomyosarcoma (11.7%), giant cell sarcoma (10.1%), and stromal sarcoma (6.2%).[6]

To date, about 70 cases are reported in literature.[4] The cellular origin of breast leiomyosarcoma has not been identified yet. It has been suggested that the tumor might originate from the smooth muscle layer of blood vessels or from myofibroblasts in the nipple areola complex that undergo myoid transformation.[7]

This tumor affects mainly middle-aged women who present with long history of breast nodules. Various risk factors are described commonly including prior history of irradiation, chronic lymphedema, vinyl chloride exposure, and Epstein-Barr (EBV) virus infection. RB1 and PTEN tumor suppressor genes are found to be associated.[8]

The natural history of leiomyosarcoma of breast is not well defined. Clinically they manifest themselves as large painless breast tumors that grow progressively, without involvement of the skin or deep layers and without nipple discharge. Axillary lymph node

involvement is rare. It disseminates through hematogenous route, giving rise to metastases in the lungs, bones, liver and central nervous system.[9]

Most leiomyosarcomas of the breast are well circumscribed tumors. Microscopically, the tumors are composed of pleomorphic and hyperchromatic spindle-shaped cells arranged in an interdigitating fascicle. The cytological features reported are hyperchromasia in the nuclei, pleomorphism and mitoses. In previous literature, the mitoses of the tumors ranged from two to 21 per 10 HPF with an average of 10 mitoses.[10]

The diagnosis of leiomyosarcoma of the breast is made on postoperative specimens by using immuno-histochemical stains. The cells are positive for SMA, vimentin and desmin and negative for epithelial markers.[11]

Treatment algorithms for breast sarcomas are based on studies related to soft tissue sarcoma of extremities. Surgical resection with negative margins remains the mainstay of treatment. Adjuvant therapy with chemo and/or radiotherapy has not proved efficient in such tumors, although some evidence has been recorded in other sarcomas that suggests that it might be useful. Lymphatic spread and nodal metastasis are not features of sarcoma so axillary dissection is not recommended.[12]

We performed Modified radical mastectomy based on oncological principles. Breast conservation surgery and WLE are other options based on size and location of growth, but the limiting factor is presence of positive margin. High-grade sarcomas have increased tendency to recur; therefore, radiotherapy is used in adjuvant setting to achieve local control and prevent recurrence. Anthracycline-based chemotherapy has been used in high-grade and bulky tumors (> 5 cm) as these have high propensity for distant metastasis. Targeted therapy in the form of pazopanib and hyperthermia has been tried in one case, efficacy of which is not yet proven.[13] So, there is a need of multidisciplinary evaluation followed by personalized approach in each case taking into account the risks and benefits associated with various treatments available.

Conclusion

Leiomyosarcoma is an aggressive tumor and a lot is still required to know about its behavior.

Conflict of Interest:

No financial disclosure

Acknowledgement:

We gratefully acknowledge the contributions of the patients.

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Review Article

Cancer J Bangladesh 2021;2(2): 31-37
http://nicrh.gov.bd/publication

HRCT- Chest Features Simulating COVID-19 Lung Disease – A Review

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Citation: Jalali MA and Parveen F. HRCT- chest features simulating COVID-19 lung disease – a review. Cancer J Bangladesh 2021;2(2):31-37.

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Received : 11 July 2021
Accepted : 03 September 2021
Published : 08 November 2021

Abstract:

HRCT (High-Resolution Computed Tomography) of chest is often used as a complementary tool in different clinical settings of coronavirus disease 2019 (COVID-19) patients, helping physicians to supplement their clinical suspicion. However, COVID-19 imaging appearance is veryinconsistent and nonspecific. Indeed, many pulmonary infections and non-infectious diseases can show similar HRCT findings and simulate COVID-19 pneumonia. This review focuses on the clinical conditions that share a similar HRCT-chest appearance with COVID-19 pneumonia, to facilitate the HRCT features and clinical characteristics useful in the differential diagnosis, encompassing both infectious etiologies, such as non-COVID viral pneumonia, Mycoplasma pneumoniae, Pneumocystis jiroveci, and pulmonary granulomatous infectious, and non-infectious disorders, such as pulmonary edema, fat embolism, cryptogenic organizing pneumonia, non-specific interstitial pneumonia, desquamative interstitial pneumonia, and acute and chronic eosinophilic pneumonia.

Keywords: *COVID-19 Lung disease, Pneumonia, Chest HRCT, Differential diagnosis*

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020. COVID-19 clinical presentation is highly variable and non-specific, with fever, cough, dyspnea, anosmia, dysgeusia, fatigue, and muscle aches being the most common symptoms. Some cases progress to a severe viral pneumonia with respiratory failure and even death, while others recover completely. Older adults and patients with multiple comorbidities have a worse outcome, as they have a higher risk of developing diffuse alveolar damage requiring mechanical ventilation. Moreover, COVID-19 infection can be asymptomatic in a significant number of cases.

The standard diagnostic method for COVID-19 infection is the reverse-transcription polymerase chain reaction (RT-PCR), which detects virus nucleotides in oropharyngeal and nasopharyngeal swab samples, bronchoalveolar lavage or tracheal aspirate.

RT-PCR testing has low sensitivity early in the disease (ranging from 37 to 71%).[1]HRCT chest has high sensitivity, but low specificity.[1-4] This low specificity may stem from the fact that it is difficult to distinguish COVID-19 from other diseases on chest HRCT.[5]

HRCT has a high sensitivity, about 94–97%,[6,7] in detecting early signs of COVID-19 pneumonia, disease

progression, complications, and possible alternative diagnoses such as heart failure or pulmonary edema.

The specificity of HRCT is low (about 37%)[6], since many lung diseases that can simulate COVID-19 pneumonia by CT appearance. Indeed, many radiology professional societies recommend against performing CT as a primary technique for the diagnosis of COVID-19 pneumonia.[10]

Chest imaging has been used as a complementary tool in the evaluation of COVID-19 including chest radiography, lung ultrasound, and HRCT scans. Even though not being definitively diagnostic for COVID-19, HRCT imaging of chest can establish the presence of lung pathology and demonstrate findings supposed typical of COVID-19.[8] In this way, patients with suggestive symptoms and imaging of COVID-19 infection can be isolated until RT-PCR test results become available. However, COVID-19 findings on HRCT can also overlap other viral infections and noninfectious etiologies, and physicians should be aware of possible mimickerspatients.[9]

This review aims to discuss the potential differential diagnoses of COVID-19 on chest HRCT and clarify the distinguishing clinical and radiological features.

COVID-19 typical CT findings:

The key imaging finding in COVID-19 pneumonia is ground-glass opacity (GGO), defined as an area of hazy increased lung attenuation which do not conceal bronchial and vascular structures.[11]

On HRCT of chest COVID-19 presentation will change according to the stage of the disease, which can be divided into early, intermediate, and late phases.[9] Not all patients will go through all these imaging stages. Although some CT scans during the early phase of the disease (0–5 days after the onset of symptoms) may be normal, there is a predominance of small areas of ground-glass opacities (GGOs) with subpleural distribution in one or, most commonly, both lungs (Figure 1). Less frequently, the chest CT may show a consolidation pattern.[9,12]

In the intermediate phase (about 6–11 days after the onset of symptoms), there is still a predominance of ground-glass pattern in most patients. However, there may be an expansion of CT findings in the pulmonary parenchyma with a higher number of GGO and bilateral involvement, as well as denser areas (foci of consolidation).In the late phase (about 12–17 days after the onset of symptoms), most patients have confluent lesions with mixed consolidation and GGO in a bilateral

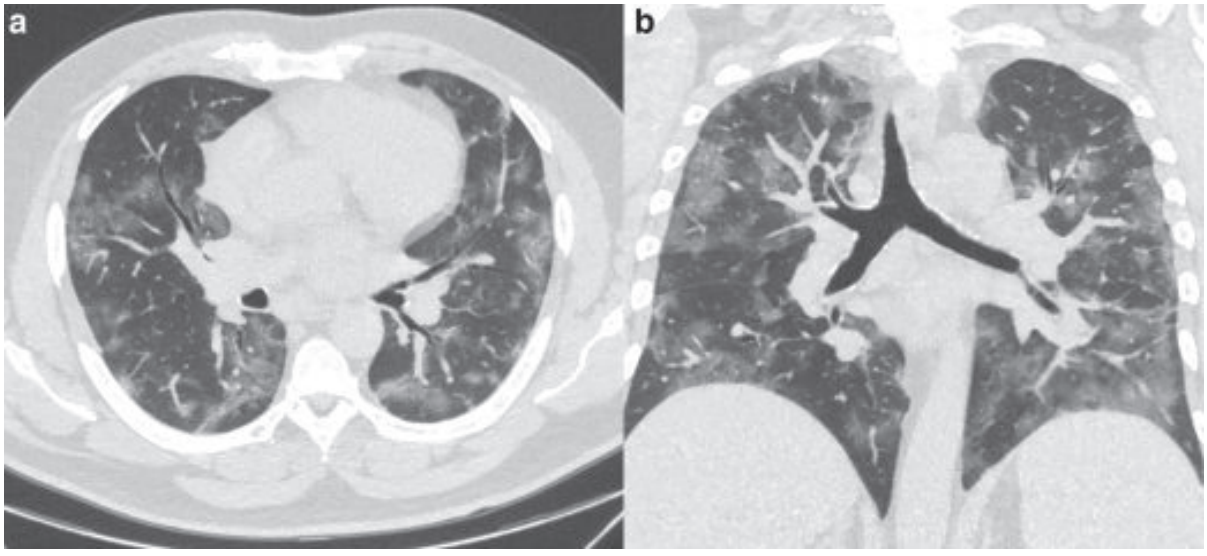

Fig.-1: *51-year-old patient presenting with CT findings of COVID-19 confirmed by RT-PCR. (a) Axial chest CT in lung windows demonstrates bilateral predominantly peripheral ground-glass attenuation without consolidation. (b) Coronal reformatted CT shows bilateral ground-glass attenuation.*

distribution. In association, there may also be inter- and intralobular septal thickening that manifests as a "crazy-paving" pattern. Less frequently, the "reversed halo sign" can also be seen in COVID-19, mainly in the intermediate to the late phase of the disease.[9,12]

Differentials of typical HRCT findings in COVID-19

Infectious etiologies that can simulate COVID-19 on HRCT

Other viral pneumonia

Viral pathogens are one of most frequent etiology of pneumonia, accounting for around 25 and 70% of cases of community-acquired pneumonia in adults and children, respectively.[13]The disease pathogenesis, age group, and immune status can provide some clues on the diagnosis. However, there are several unspecific findings on HRCT scans, that may overlap with other lung conditions.In general, viral pneumonia presents as multifocal (random or segmental) findings with GGO and consolidations (Figures 2). A recent meta-analysis with 2263 patients reported overlapping CT findings between COVID-19 and other viral pneumonia, including high prevalence of a mixed pattern of GGO and consolidation, bilateral distribution, and involvement of lower lobes.[13] On the other hand, COVID-19 pneumonia presented a higher prevalence of peripheral distribution, and involvement of upper and middle lobes when compared to other viral pneumonia.[13]

Although rare in COVID-19, bronchial wall thickening, and pleural effusion are common findings in infections by adenovirus, parvovirus, paramyxovirus (measles), herpes (HSV), hantavirus, and phenuivirus.[14] Hantaviruses infections and COVID-19 may have a shared CT finding as interlobular septal thickening. Pulmonary micronodules and larger nodules are predominantly seen in adenoviruses, herpes (Herpes virus and varicella-zoster), paramyxovirus (measles), pneumovirus, and orthomyxovirus, and are uncommon in COVID-19 patients.[14]

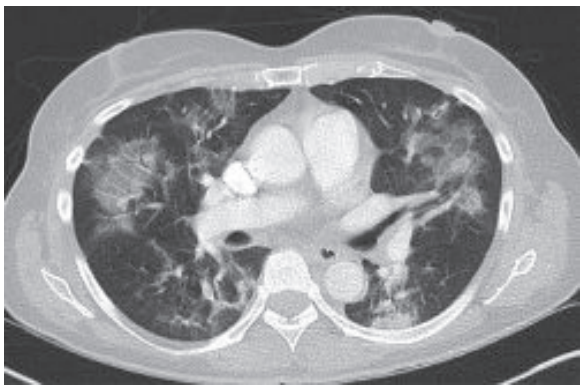

Fig.-2: *58-year-old male with Influenza A H1N1 pneumonia. Axial CT image demonstrates a predominant pattern of consolidation with diffuse distribution, air bronchograms, and sparse ground-glass opacities.*

Mycoplasma pneumoniae infection

Mycoplasma pneumoniae is a frequent cause of pneumonia, especially in children and young adults. However, it may affect all ages, regardless of the patient's immune status. Pneumonia is the most common clinical manifestation in school-aged children, and common symptoms include fever, non-productive cough, fatigue, dyspnea, headache, and sore throat.[15] Typical HRCT findings include bronchial wall thickening and centrilobular nodules, as well as GGO and consolidations, commonly affecting more than one lobe (Figure 3). Less frequently, it demonstrates reticular or linear opacities, lymphadenopathy, and pleural effusion.[14] Centrilobular nodules and bronchial wall thickening are commonly seen in *Mycoplasma pneumoniae* infections but are uncommon in COVID-19.

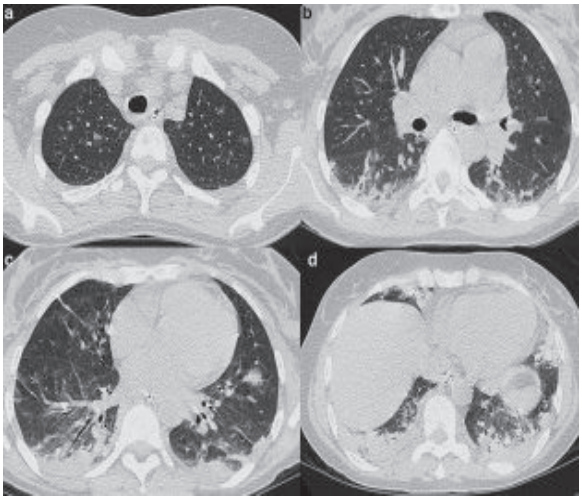

Fig.-3: *48-year-old female with non-Hodgkin lymphoma and Mycoplasma pneumoniae infection. (a–d) Axial HRCT images demonstrate random centrilobular nodules with ground-glass and solid attenuation, bronchial wall thickening and consolidations predominantly in the lower lobes.*

Pulmonary *Pneumocystis jiroveci* infection

Pneumocystis jiroveci pneumonia (PJP) is an opportunistic disease usually affecting immunocompromised patients with CD4 lymphocyte counts lower than 200 cells/microL and especially under 100 cells/microL. (CD4 cell count is normally between 400 and 1400 cells/μL).

When immunosuppression is known, there is a higher chance of distinguishing PJP from COVID-19, although CT scans may be similar. While COVID-19 has a CT predominance of multifocal and peripheral GGOs, the main pattern of PJP is represented as a central and diffuse distribution with relative subpleural sparing (Figure 4).[15] Both conditions can present with some degree of consolidations, interlobular septal thickening, and "crazy paving pattern". Around one-third of PJP cases present pulmonary cysts with variable shape, wall thickness, and size,[15] findings that have not been reported in COVID-19.

Infectious pulmonary granulomatous disease

There are a considerable number of etiologies for granulomatous pulmonary disease, both infectious or noninfectious, and therefore chest HRCT scans can show different patterns of presentation. Some of these findings are commonly seen in COVID-19 CT scans and may confound radiologists and clinicians in determining the correct diagnosis. As demonstrated in COVID-19, HRCT finding in granulomatous diseases include GGOs, especially in paracoccidioidomycosis (Figure 5). A reversed halo sign may also be present in tuberculosis[16], among others. Clinical, laboratory and immune status details are indispensable for investigating the etiology in order to differentiate from COVID-19.

Non-infectious etiologies that can simulate COVID-19 on Chest HRCT

Fat embolism

Fat embolism usually occurs as a rare complication of long bone fracture with a prevalence of 1–3% of patients with tibial or femoral fractures and 20% in more severe osseous polytrauma.[17] The classical clinical triad consists of respiratory distress, cerebral abnormalities, and petechial hemorrhages. Pulmonary fat embolism can present at CT as areas of GGO with interlobular septal thickening, ground-glass changes with patchy distribution resulting in a geographic appearance, or as nodular opacities without any zone predominance.[18] Therefore, some CT findings may overlap with COVID-19 presentation. However, the clinical history of recent long bone fracture, trauma, or surgical fixation can assist the differentiation.

Non-infectious organizing pneumonia

The organizing pneumonia pattern is the imaging representation of a healing process. Cryptogenic organizing pneumonia is an interstitial lung disease that represents the idiopathic form of this CT pattern. Patients are usually between 50 and 60 years old, equally

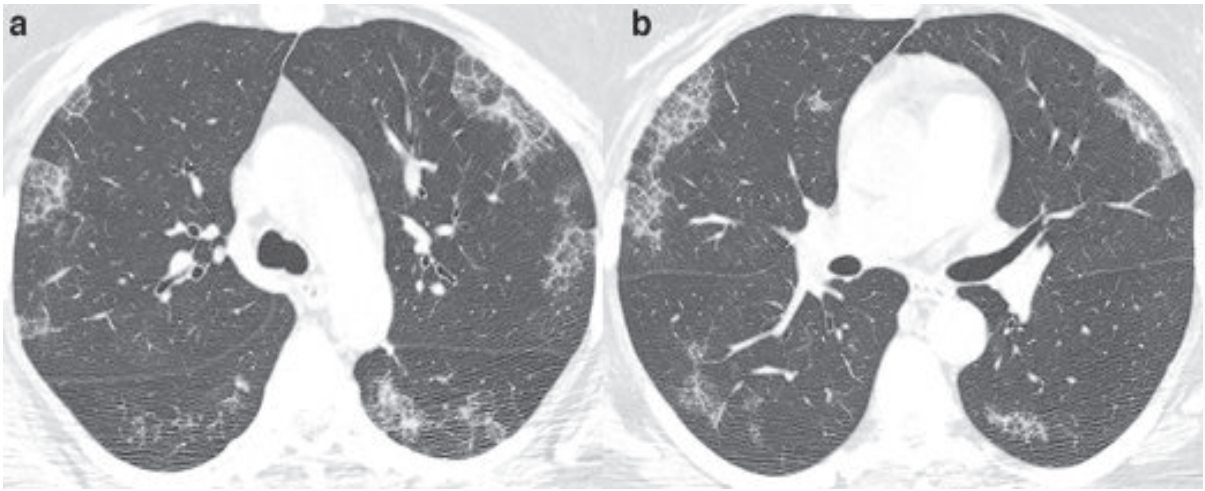

Fig.-4: *32-year-old male with acquired immuno-deficiency syndrome and Pneumocystis jiroveci pneumonia. (a, b) Axial CT images demonstrate ground-glass opacities and intralobular septal thickening in the periphery of the upper lobes and the superior segments of the lower lobes.*

affecting males and females. They may present with subacute symptoms, such as cough, mild dyspnea, fever, malaise, and sometimes weight loss. [19,20] HRCT imaging is mostly polymorphic, characterized by a mixed pattern of consolidation and GGO, that may be single or multiple, with a focal, bronchocentric, or subpleural distribution.[31] Moreover, there may be a nodular or crazy paving pattern and reversed halo sign. Due to its several forms of presentation, organizing pneumonia may have a considerable number of differential diagnoses other than infections, such as drug toxicity, immune diseases, actinic lesions, among others.

Non-specific interstitial pneumonia

Non-specific interstitial pneumonia (NSIP) is one of the most common interstitial lung disease patterns in chest CT. NSIP is usually associated with connective tissue diseases (CTD), such as systemic sclerosis, Sjögren syndrome, polymyositis, and dermatomyositis. NSIP can also be due to HIV infection or be idiopathic.[19,21]

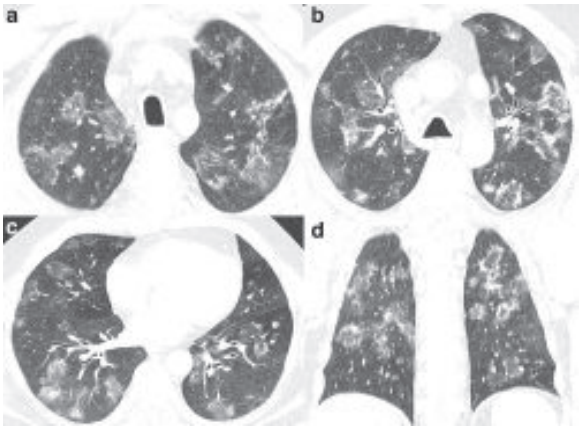

Fig.- 5. *58-year-old male with paracoccidioidomycosis. (a–c) Axial and (d) coronal CT images demonstrate diffuse ground-glass lesions in a random distribution, some with a peripheral rim of consolidation yielding the reversed halo sign and some solid nodules.*

Chest CT often demonstrates a subpleural, bilateral, and lower lobe predominance of ground glass with or without reticular abnormalities and mild subpleural fibrosis (Figure 6). Therefore, the ground-glass component can be considered an alternative diagnosis for COVID-19.[22]However, the ground glass areas are less geographic, and there are nearly always some

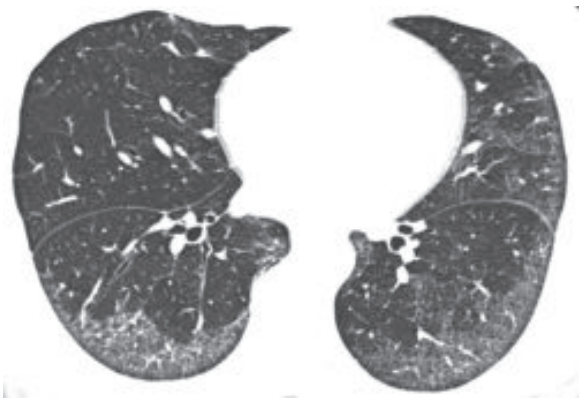

Fig.-6: *High-resolution CT shows predominantly subpleural and basilar ground-glass opacities. The relative sparing of the lung directly beneath the pleural surfaces is typical in nonspecific interstitial pneumonia.*

components of subpleural fibrotic findings, such as subpleural reticulation, with fibrotic subtype also having traction bronchiectasis and volume loss of the affected lobe.

Desquamative interstitial pneumonia

Desquamative interstitial pneumonia (DIP) is seen predominantly in smokers. Chest HRCT shows subpleural and bilateral ground-glass opacities frequently associated with irregular linear opacities predominantly involving the lower lobes.[19] Due to the peripheral, diffuse, and bilateral involvement of pulmonary parenchyma in chest CT, generally with GGO, desquamative interstitial pneumonia may also be considered a COVID-19 differential diagnosis in early stages, even though, as other pathologies, the disease's course and tobacco use can help in the diagnosis.

Acute and chronic eosinophilic pneumonia

Eosinophilic lung diseases are a heterogeneous group of disorders marked by lung opacities with tissue or peripheral eosinophilia. Regarding the disease onset, they can be divided into acute and chronic eosinophilic pneumonia. Tobacco smoking is the most frequently implicated trigger. Males and females equally affected. On chest HRCT imaging, acute eosinophilic pneumonia present patchy areas of GGO accompanied by consolidation opacities and smooth interlobular septal thickening (Figure 7), findings that overlap with COVID-19 pneumonia.[23] Thickening of bronchovascular bundles, lymph node enlargement, and pleural effusions are also common findings.

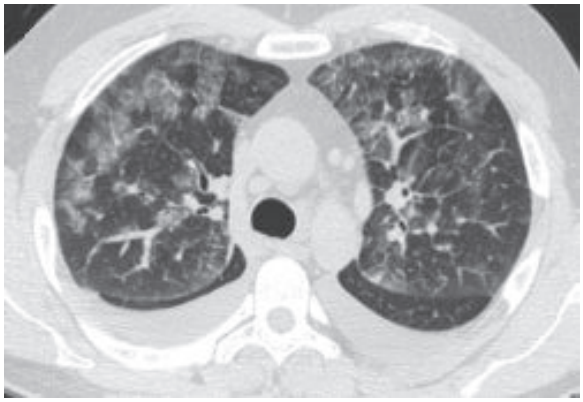

Fig.-7: *HRCT findings in a 45-year-old patient with smoking-related acute eosinophilic pneumonia. The patient had resumed cigarette smoking for the past 2 weeks after several years of abstinence. The axial views of upper lungs demonstrate bilateral patchy ground-glass opacities associated with interlobular septal thickening and bilateral pleural effusions.*

Chest HRCT in chronic eosinophilic pneumonia mostly demonstrates non-segmental areas of airspace consolidation with peripheral predominance. GGO, nodules, reticulation, and pleural effusions are rare findings in the chronic phase.[24]

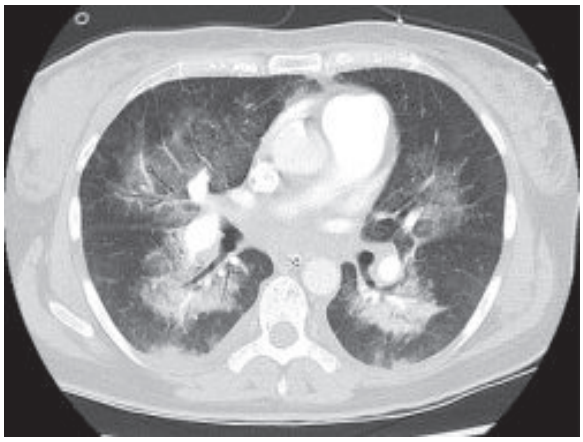

Fig.-8: *HRCT findings in a 40-year-old patient with pulmonary edema Bilateral ground glass opacity in a central peribronchovascular distribution classic of acute pulmonary oedema. There is also smooth thickening of the interlobular septae.*

Pulmonary edema

Pulmonary edema has various types and etiologies with different radiological patterns: cardiogenic pulmonary edema (e.g., congestive heart failure), non-cardiogenic pulmonary edema and fluid overload (e.g., renal failure).[25] Both pulmonary edema and COVID 19 infection may have bilateral GGO but with different distribution and other associated signs. The diffuse ground-glass pattern of cardiogenic pulmonary edema tends to be perihilar, bilateral and symmetrical (Fig. 8). Cardiogenic pulmonary edema is presented by acute dyspnea, associated with cardiomegaly and pleural effusion is common, while ARDS has dense-dependent consolidations, with or without interlobular septal thickening, and pleural effusion may occur.[25,26] Pulmonary edema can also be presented by crazy paving pattern.[26]

Conclusion:

A broad spectrum of pulmonary conditions demonstrates chest-HRCT features that simulate those of COVID-19 and are difficult to differentiate from it. As the infectivity rate of COVID-19 is high, it is essential not only to prepare health-care systems in order to manage all infected patients but also to conclude the right diagnosis. which will reduce acute care burden when diseases are identified as chronic or guide alternative management in other acute infections. Despite not being diagnostic for COVID-19, HRCT- chest may help clinicians to isolate high suspicion patients with suggestedHRCT findings. There are a large number of differential diagnoses for COVID-19 on chest HRCT scans, and clinicians and radiologists must be aware of these conditions. The careful consideration of acuity of symptoms and patient history with the knowledge of chest HRCT patterns in COVID-19 and its primary clinical confounders is indispensable for making the right diagnosis.

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