ALKALINE PHOSPHATASE;
TOTAL SERUM ALKALINE PHOSPHATASE (ALP) AS A PREDICTOR OF BONE METASTASIS AMONG PATIENTS HAVING CARCINOMA BREAST AT A TERTIARY CARE HOSPITAL.

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ABSTRACT… Background: This study was carried out to determine the role of total serum alkaline Phosphatase in bone metastasis among patients of breast cancer. **Setting;** Department of Surgery, Nishtar Medical University, Multan in collaboration with breast clinic MINAR. **Study Duration;** January 2016 to June 2017 **Subjects and methods;** It was a retrospective study carried out at breast clinic MINAR, Multan. The medical record of the female patients having breast cancer aged 25 to 70 years (who presented from January 2016 to June 2017) was scrutinized. All the registered patients during above mentioned period having breast carcinoma with metastatic bone disease, as depicted on bone scan, were taken as index cases. All the cases underwent total serum alkaline Phosphatase estimation. We collected 86 cases for this research study. Primary bone tumours, lymphomas, sarcomas and bone metastasis due to other primary visceral malignancies were excluded. All the required data were entered and analyzed using computer program SPSS version 20.0. **Results;** The mean age of the breast cancer patients was 46.51 ± 11.11 years (ranging from 25 – 70 years). Eighty four (97.7%) were married. All the patients presented with lump breast. Only 3 (3.5%) of the cases gave family history of breast cancer and history of contraceptive pills was positive in 4 (3.7%) of the cases. History of breast feeding was positive in 63 (73.3%) of the cases. Mean age at menarche was 13.21± 0.896 years in our study cases. Mean age at menopause in our study was 46.86 ± 5.66 years. Total serum alkaline Phosphatase was raised in 27 (31.4%) cases. Only 6 (6.9%) of the cases showed its level more than 500 IU/L. **Conclusion;** Our study results don't favor total serum alkaline Phosphatase estimation as biological marker of bone metastasis among breast cancer patients. Bone scan is more reliable and hence be employed for detection of bone metastasis. Further studies on bone ALP and total ALP estimation are required to generate further evidence on this subject.

Key words: Serum Alkaline Phosphatase, Breast Cancer, Bone Metastasis.

INTRODUCTION

Breast cancer is the commonest cancer among females globally as well as nationally. It is the leading cause of cancer deaths in women.[1,2] Breast cancer accounts for 22% of all female cancers worldwide and approximately 42% cases occur in the developing countries.[6] In USA, it has been found that 60% of patients have benign breast disease and 10% have malignancy.[7] In Pakistan, a study carried out in 2001 reported a very low incidence of breast cancer (6%)[8], while another study in 2003 reported a frequency of 24.2%. A study from Karachi, at Jinnah Postgraduate Medical Centre, in 2005 showed that 30% of malignancies among females occur in the breast.[9] There is also geographic variation, with the standardized age incidence rate being lower in developing than industrialized countries.[10] The new millenniums still find breast cancer as a leading cause of cancer related death among females. It is expected that the number of new cases may rise to 15 million by 2025, with 60% of the cases occurring in developing countries.[9] The disease occurs commonly among females but may also occur very less frequently in males.[3,4] It is seen that if 100 female patients present with breast complaints, then among them 30% may have no breast lesion, 40% may have fibrocystic changes, 7% may have benign tumor and 10% may have carcinoma.[5,10]

Breast carcinoma spreads either regionally (to regional lymph nodes) or systemically. It most frequently metastasizes to bones in addition to lung, liver and brain.[11,12,13]

For staging and for therapeutic options for breast carcinoma it is necessary to detect the bone metastasis in these cases. Various tests are used to detect bone metastasis and simplest of all is total serum alkaline Phosphatase estimation. It is also raised in obstructive hepato-billiary disease, bone fractures, pregnancy, in growing children and even in old age. Some of these conditions are ruled out on history and some by other parallel tests like estimation of gama GT, bone Skiagrams and liver ultrasonography. The gold standard test for bone metastatis detection is bone scan, however total serum alkaline Phosphatase is still being used as basic test for prediction of bone metastasis in some countries. If it is raised two times above normal or more than this, it is taken as abnormal and points towards some pathology. In patients of carcinoma breast its raised level points to some bony involvement and[14] levels above 500 IU/L raises the possibility of bone mets[15], however may remain even normal in some cases of breast cancer with metastatic bone disease.[16] The same trend was observed at our breast clinic during the evaluation of breast cancer patients. So the present study was carried out to detect the significance of total Serum Alkaline Phosphatase estimation in prediction for bone metastasis in patients of breast carcinoma at a tertiary care hospital.

SUBJECTS AND METHODS

It was a retrospective study carried out at breast clinic MINAR, Multan. The medical record of the female patients having breast cancer aged 25 to 70 years (who presented from January 2016 to June 2017) was scrutinized. All the registered patients during above mentioned period having breast carcinoma with metastatic bone disease, as depicted on bone scan were taken as index cases. All the patients also underwent total serum alkaline Phosphatase estimation. We collected 86 cases for this research study. Primary bone tumours, lymphomas, sarcomas and bone metastasis due to other primary visceral malignancies were excluded. All the required data was entered and analyzed using computer program SPSS version 20.0.

RESULTS

We examined medical record of 86 index cases. The mean age of the breast cancer patients was 46.51 ± 11.11 years (ranging from 25 – 70 years). Eighty four (97.7%) were married. All the patients presented with lump breast. Only 3 (3.5%) of the cases gave family history of breast cancer and history of contraceptive pills was positive in 4 (3.7%) of the cases. History of breast feeding was positive in 63 (73.3%) of the cases. Mean age at menarche was 13.21 ± 0.896 years in our study cases. Mean age at menopause in our study was 46.86 ± 5.66 years. Total serum alkaline Phosphatase was raised in 27 (31.4%) cases. Only 6 (6.9%) of the cases showed its level more than 500 IU/L.

DISCUSSION

Breast carcinoma starts from the breast tissue at cellular level. The cells lining the ducts, tubules or any other tissue in the breast may develop malignant change and lead to carcinoma of breast. The malignant cell proliferates into a group of cancer cells that can grow locally and invade the surrounding tissues or spread (metastasize) to distant areas of the body. Bone metastases are common in breast cancer and develop in approximately 70 % of patients with metastatic breast cancer.

In our study, mean age of the patients was 46.51 ± 11.11 years (range; 25 – 70 years). Similar results have been reported by various researchers from Pakistan showing prevalence of the disease in middle of 4th decade of their life. Memon et al[17] from Karachi reported 47.8 ± 12.4 years mean age of women with breast cancer. Another study[18] from Karachi reported 47.5 ± 12.1 years mean age of patients presenting with breast cancer. The findings of both these studies are close to that of our study. Similar findings have been reported by Nazir et al[19] and Nisar et al.[20]

In our study family history of breast cancer was positive 3.5 % which is quite less than that reported from other studies in Pakistan. A study conducted by Memon et al[17] from Karachi reported 13.3 % positive family history. Another study from Karachi[18] reported 20 % patients of breast cancer had positive family history. The same figures have been reported by Faheem et al.[21] A study by de Bruin MA et al[22] reported as high as 50 % family history of breast cancer in Asian women. The different findings may be due to differences in cultural, social, lifestyle and living standards. Moreover females in our study may be more shy, less responsive to the data collector and less educated. Lack of awareness about this disease entity may be another possible reason.

History of breast feeding was positive in 73.3 % in our study cases. Various studies have reported history of breast feeding differently, in some studies it is 61 % and in another study 42 % Memon et al[17] and de Bruin MA et al[22] respectively. These differences may be again due to cultural variations. Moreover, our study patients were house-wives and jobless and from poor socioeconomic status, so they were unable to afford formula milks.

Mean age at menarche was 13.21± 0.896 years in our study cases while Memon et al[17] from Karachi reported 12.96±1.60 years mean age at menarche. The same findings have been reported by Nazir et al.[19] These both findings are in consonance with our study results.

Mean age at menopause in our study was 46.86 ± 5.66 years which is in compliance with other studies conducted by Memon et al[17] from Karachi who reported 46.35 ± 6.65 years mean age of the ladies with breast cancer.

Alkaline Phosphatases and its various iso-enzymes are phosphatidylinositol anchored cell membrane proteins. Raised serum ALP has various clinical implications. It is raised in various conditions like intra and extra hepatic billiary obstruction, infiltrative liver disease, bone mets and cancers. ALP estimation is an inexpensive and is used in various developing countries as a potential biological marker. In some studies on breast cancer its parallel rise with advancing disease has been noted.[23] In our study, total serum alkaline phosphatase level was raised in 31.4% of patients while its level more than 500 IU/L was noted in 6.9 %.

In a study conducted by Singh et al[23] its level more than 500 IU/L have been reported in 61 % of the patients in stage 4 of breast carcinoma cases and its rise strongly relates to bone mets. Singh et al[23] further stated that progressive increase in ALP is an indication of bone metastasis in breast cancer patients. Mayne et al[24] also reported increase in total alkaline phosphatase in 20 % of patients with breast cancer.

Sandhya et al[25] reported a significant rise to 6 fold of ALP normal levels in metastatic patients with breast carcinoma. The findings of our study are not in agreement with the study conducted by Singh et al[23] and Sandhya et al[25], it may be due to the reason that the patients in our study may not have so advanced disease. Total ALP may be useful diagnostic tool in monitoring the activity of the disease where sophisticated tools are not readily available moreover its estimation is simple and cost-effective but its significance in detection of bone mets remains controversial.

With the recent advent of more specific immune-assays like bone ALP estimation has gained clinical interest and several studies have indicated that in certain situations bone ALP might provide better index of bone formation than measurement of total ALP. They also reported that bone ALP was more frequently raised in bone metastatic disease of prostatic cancer patients compared to the patients of breast cancer or lung cancer with bone mets. So, bone alkaline Phosphatase estimation might have provided better picture on this subject than total ALP but this test was not available in our setting so total serum alkaline Phosphatase was estimated in our study cases.

CONCLUSION
Our study results don't favor total serum alkaline

Phosphatase estimation as biological marker of bone metastasis among breast cancer patients. Bone scan is more reliable and hence be employed for detection of bone metastasis. Further studies on bone ALP and total ALP estimation are required to generate further evidence on this subject.

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REFERENCES

1. DeSantis C, Siegel R, Bandi P, Jemal A. **Breast Cancer Statistics, 2011: American Cancer Society.** CA Cancer J Clin. 2011; 61(6):408-18.

2. Sohail S, Alam SN. **Breast Cancer in Pakistan-Awareness and Early detection.** J Coll of Physicians Surg Pak. 2007; 17(12):711-2.

3. Giordano SH, Cochen DS, Buzdar AU, Perkins G and Hortobagyi GN. **Breast Carcinoma in men: a population based study.** J Cancer. 2004; 101(1):51-7.

4. Shami SA, Jalali S, Niazi SF. **Epidemiology of Breast Cancer findings from Hospital Patients.** Pak Armed Forces Med J. 1999; 49(2):97-8.

5. Khatib OMN, Modjtabai A. **Guidelines for the early detection screening of breast cancer by WHO Regional Office for the Eastern Mediterranean.** 30th ed. Cairo: EMRO Technical Publication Series; 2006.

6. Parkin DM, Bray F, Ferlay J, Pisani P. **Estimating the world cancer burden: Globocan 2000.** Int J Cancer. 2001; 94:153-6.

7. Kumar V, Abbas AK, Fausto N, Aster J. **Robin's pathologic basis of disease.** 4th ed. Philadelphia: WB Saunders 1989; 1181-1204.

8. Siddiqui K, Rasool MI. **Pattern of breast diseases: preliminary report of breast care clinic.** J Coll Physicians Surg Pak. 2001; 11(8):497-500.

9. Issac U, Memon F, Zohra N. **Frequency of breast diseases at a Tertiary Hospital of Karachi.** J Liaqat Uni Med Health Sci. 2005; 4(1):6-9.

10. Gezairy HA. **Guidelines for management of breast cancer by WHO Regional Office for the Eastern Mediterranean.** 31st ed. Cairo: EMRO Technical Publication Series; 2006.

11. Palma MA1, Body JJ. **Usefulness of bone formation markers in Breast Cancer.** Int J Biol Markers. 2005 Jul-Sep; 20(3):146-55.

12. Sarvari BK1, Sankara Mahadev D2, Rupa S3, Mastan SA4. **Detection of Bone Metastasis in Breast Cancer Patients by Serum Tartarate-Resistant Acid Phosphatase 5b (TRACP 5b), a Bone Resorption Marker and Serum Alkaline Phosphatase (ALP), a Bone Formation Marker, in Lieu of Whole Body Skeletal Scintigraphy with Technetium99m MDP.** Indian J Clin Biochem. 2015 Jan; 30(1):66-71.

13. Baker RR. **Preoperative assessment of the patient with breast cancer.** Sug Clin North Am. 1978 Aug; 58(4):681-91.

14. White DR, Maloney JJ £rd, Muss HB, Vance RP, Barnes P, Howard V, Rhyne L, Cowan RJ. **Serum alkaline phosphatase determination. Value in the staging of advanced breast cancer.** JAMA 1979 Sep 14; 242(11):1147-9.

15. A.K.Singh, A. Pandey, […], and H. S. Shukla. **Advanced stage of breast cancer hoist alkaline phophatase activity: risk factor for females in India.** 3 Biotech. 2013 Dec; 3(6): 517-520.

16. Lee YT. **Bone scanning in patients with early breat carcinoma: Should it be a routine staging procedure?** Cancer 1981 Feb 1:47(3):486-95.

17. Memon ZA1, Qurrat-ul-Ain, Khan R, Raza N, Noor T. **Clinical Presentation and Frequency of Risk Factors in Patients with Breast Carcinoma in Pakistan.** Asian Pac J Cancer Prev. 2015;16(17):7467-72.

18. Memon ZA1, Shaikh AN, Rizwan S, Sardar MB. **Reasons for patient's delay in diagnosis of breast carcinoma in Pakistan.** Asian Pac J Cancer Prev. 2013; 14(12):7409-14.

19. Nazir N, Waheed A, Farhat K, Ismail M, Mansoor Q, Javed G. **A case control study of risk factors of female breast cancer.** Pak Armed Forces Med J. 2015; 65(3):391-96.

20. Nisar A, Siddiqi MN, Naveed ur Rehman, Raza ur Rehman. **Breast cancer; frequency of risk factors.** Professional Med J 2014; 21(6):1128-1132.

21. Faheem M, Khurram M, Jafri IA, Mehmood H, Hassan Z, Iqbal GS, et al. **Risk factors for breast cancer in patients treated at NORI Hospital, Islamabad.** J Pak Med Assoc. 2007; 57(5):242-4.

22. de Bruin MA1, Kwong A, Goldstein BA, Lipson JA, Ikeda DM, McPherson L et al. **Breast cancer risk factors differ between Asian and white women with BRCA1/2**

mutations. Fam Cancer. 2012 Sep; 11(3):429-39.

23. Singh AK[1], Pandey A[1], Tewari M[1], Kumar R[2], Sharma A[2], Singh KA[3], et al. **Advanced stage of breast cancer hoist alkaline phosphatase activity: risk factor for females in India.** 3 Biotech. 2013 Dec; 3(6):517-520.

24. Mayne PD, Thakrar S, Rosalki SB, Foo AY, Parbhoo S. **Identification of bone and liver metastases from breast cancer by measurement of plasma alkaline phosphatase isoenzyme activity.** J Clin Pathol. 1987 Apr; 40(4):398-403.

25. Mishra S[1], Sharma DC, Sharma P. **Studies of biochemical parameters in breast cancer with and without metastasis.** Indian J Clin Biochem. 2004 Jan; 19(1):71-5.
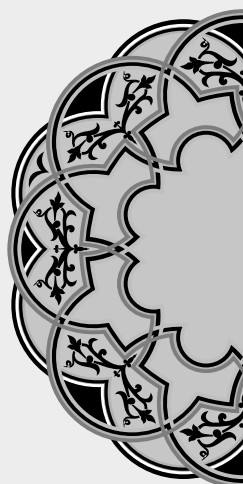
"A women is unstoppable after she realizes she deserves better."

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Fariha Ahmed	Studyplanning, designing, data entry manuscript writing and editing.	
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