Role of Platelet Counts in Prognostication of Head And Neck Squamous Cell Carcinoma.

Wasim M. Khatib[1], Dhirajkumar B. Shukla[1], Sujata R. Kanetkar[2], Atul B. Hulwan[3], Pradnya P. Kale[3]

[1]*Assistant Professor, Department Of Pathology, Krishna Institute Of Medical Sciences, Karad*
[2]*Professor And Head, Department Of Pathology, Krishna Institute Of Medical Sciences, Karad*
[3]*Resident, Department Of Pathology, Krishna Institute Of Medical Sciences, Karad*

Abstract:
Background:Squamous cell carcinoma of head and neck region is a common malignancy in India. To reduce the morbidity and mortality due to this malignancy newer prognostic markers are required. Pre-treatment thrombocytosis is a poor prognostic marker.
Material & Methods: Present study is a prospective, cross sectional, analytical 3 years study undertaken in Department of Pathology, Krishna Institute of Medical Sciences, from June 2012 to May 2015. Pre- treatment platelet counts, age, gender site, tumor size, grade, stage, lymph node involvement, degree of penetration & vascular invasion were correlated and studied to find association between mean platelet count and individual parameters.
Result: 107 cases of Head &Neck Squamous Cell Carcinoma were studied. Mean age was 58 years with men most commonly affected and most patients being in stage II. Majority of the tumors were in oral cavity. Statistical correlation was done of mean platelet count with gender, age, site and lymph node involvement, degree of penetration, distant metastasis & presence of vascular involvement. Significant correlation was observed between platelet count, lymph node involvement and degree of differentiation. Patients having higher platelet count had unfavourable prognosis.
Conclusion: Thrombocytosis is poor prognostic factor in head and neck Squamous Cell Carcinoma. Significant association was found between degree of differentiation, lymph node involvement and mean platelet counts.

I. Introduction

Head and neck squamous cell carcinoma is associated with significant morbidity and mortality rate. It is one of the most common malignancies across the world and is mainly linked to tobacco smoking, Human Papilloma Virus and alcohol consumption.[1] Apart from these factors recent studies have shown certain haematological parameters which include neutrophils, lymphocytes, monocytes and platelets which can predict the prognosis of the malignancies.

Numerous studies have shown pre-treatment thrombocytosis to correlate with shorter survival and hence proved to be a poor prognostic indicator in a number of malignancies. [2,3,4,5] Surgery is the preferred treatment for these malignancies. However, even after great progress in chemotherapy, radiotherapy and targeted therapy, prognosis of head and neck squamous cell carcinoma is poor owing to aggressive local invasion and metastasis leading to recurrence.

II. Material & Methods

Present study is a prospective study of 3 years from June 2012 to May 2015. Small biopsies, wide excisions and neck dissections received in the department of Pathology, KIMS, Karad related to the region of head and neck were processed by routine histopathology techniques like processing & staining with routine Haematoxylin &Eosin stain. Microscopically, the cases diagnosed as squamous cell carcinoma, were included in the study with following criteria:

Inclusion Criteria: Primary squamous cell carcinoma from head and neck Exclusion Criteria: Lesions other than Primary squamous cell carcinoma Patients with platelet disorders.

Metastatic SCC from other sites were excluded from the study.

107 patients diagnosed with primary squamous cell carcinoma of head and neck region during this period were analysed statistically. The cases positive for squamous cell carcinoma were further analysed with tumor differentiation, vascular invasion, lymph node metastasis. Clinical details like age, sex along with pre-operative platelet counts of such cases were obtained. The platelet counts of these cases were obtained by staining the peripheral blood smears with Leishman staining. The association of platelet count in prognosis with relation to

age, sex, degree of differentiation, vascular invasion, lymph node metastasis, recurrence and survival of such cases was noted.

III.   Results

A total of 107 cases of head and neck squamous cell carcinoma were studied which were received at Department of Pathology KIMS, Karad over a period of 3 years. Of the 107 cases 68(63.55%) were male & 39(36.44%) were female. Male to female ratio was 1.7:1. The platelet counts were divided into low, high normal & high, with low platelet count being less than 1.5 lakh/cumm, high normal 3.15- 3.99 lakh/cumm , high more than 4 lakh/cumm. The most common age group affected was 7th decade with 31 (28.9 %) cases, followed by 6th decade 28(26.16%) cases. The youngest patient was a 22 years male & oldest was a 88 year female. Oral cavity was the most common site affected with 92 (85.98%) cases, followed by larynx with 10 (9.3%) cases. We had 3 cases of pharynx & 2 cases of squamous cell carcinoma over scalp (Table No. 1).

Table No. 1 Showing Distribution of cases with clinical parameters and mean platelet values

Clinical variable	Number of cases	Mean platelet count in lakh/cumm
Gender : Male Female	68 (63.55%) 39 (36.44%)	3.30 2.85
Location: Oropharynx Larynx Pharynx Skin	92 (85.98%) 10 (9.3%) 03 (2.80%) 02(1.86%)	2.70 4.55 2.33 2.32
Degree of differentiation: Well differentiated Moderately differentiated Poorly differentiated	62 (57.94%) 34 (31.77%) 11 (10.28%)	2.90 3.85 4.96

We segregated the tumors according to differentiation into well, moderate & poorly differentiated squamous cell carcinoma. 62 (57.9%) cases were well differentiated carcinoma, 34(31.77%) moderately differentiated, whereas 11 (10.28%) were poorly differentiated carcinoma. In the oral cavity 55(59.78%) were well differentiated, 32 (34.78%) cases were moderately differentiated, 5(5.43%) were poorly differentiated (Table No. 1)

Among laryngeal lesions, majority were poorly differentiated squamous cell carcinoma with 6(60%) cases followed by well differentiated lesions which comprised of 3(30%). There was a single case of moderately differentiated squamous cell carcinoma of larynx.

Well differentiated squamous cell carcinoma was predominant in pharynx; there was no poorly differentiated pharyngeal Squamous cell carcinoma in our study.

We have seen significant association between mean platelet value with lymphatic invasion and distant metastasis. (Table No. 2)

Among all the cases, 6 cases of oral cavity and a single case of larynx showed recurrence. However there was not a single case of pharynx which recurred. The mean platelet value in both these sites in recurrence cases was in the range of 3- 3.5 lakhs/cumm. (Table No. 3)

We applied Chi Square test and evaluated the association between degree of tumor differentiation and thrombocytosis which was significant in poorly differentiated cases with *p* value 0.05. (Table No. 4)

Table No. 2 Showing cases of tumor invasion with mean platelet values

Different parameters of tumor aggression	Number of cases	Mean platelet value in lakh/ cumm
Lymphatic Invasion: Present Absent	41 66	4.46
Vascular invasion: Present Absent	21 86	3.45
Distant metastasis	08 (out of 41 cases of LN invasion)	4.69

Table No. 3 Showing Recurrence with site and mean platelet value

Site	Moderately differentiated cases	Poorly differentiated cases	Mean platelet value in lakh/cumm
Oral	4	2	3.30
Pharynx	0	0	-
Larynx	0	1	3.0

Table No. 4 Showing association between thrombocytosis and grade of tumor

Degree of tumor	No. of Cases	Mean platelet value	Association (p value)
Well	62	2.90	0.065
Moderate	34	3.85	0.61
Poor	11	4.96	0.05

IV. Discussion

The relation between circulating platelets & carcinoma progression suggest that platelets have a more important role beyond just the hemostatic function. [6, 7] Platelets act as a mediators of angiogenesis, wound healing & immune modulation. They secrete cytokines & growth factors such as TGF β, VEGF, MMP-2, PF-4 & PDGF. [8,9,10,11] All the above mentioned factors induce carcinoma progression such as epithelial, mesenchymal transition, angiogenesis, cell migration& proliferation.[12] Platelet derived TGF β promotes carcinoma metastasis which inturn produces soluble mediators such as IL-6, GMCSF which in turn stimulate thrombopoiesis. [13,14,15,16]

We investigated relationship between platelet count in peripheral venous blood & clinical outcome in terms of site of tumor, grade of tumor, presence of vascular invasion & presence or absence of lymphnode distant metastasis. According to Wang B et. al. male to female ratio of head and neck squamous cell carcinoma is 1.9:1 with most commonly affected age group being 6th decade. [17]

Pre treatment thrombocytosis has proven to be an independent prognostic factor for poor outcome which was observed in our study. Recurrence of tumor was noted in 7cases. Less follow up time could be the reason of low recurrence. Among the cases, 6 were of oral cavityof which 2 cases had poorly differentiated squamous cell carcinoma & 4cases had moderately differentiated squamous cell carcinoma as primary diagnosis.

On follow up, 11 cases died out of which 6 cases had poorly differentiated squamous cell carcinoma, whereas 5 had moderately differentiated squamous cell carcinoma. Mean platelet volume in all the cases which were poorly differentiated was 4.96 lakh/cumm, where as in moderately differentiated squamous cell carcinoma the mean platelet volume was 3.85 lakh/cumm. All the well differentiated squamous cell carcinoma cases had platelet values within the normal category i.e. 2.90 lakh/cumm.

Statistical analysis revealed that poorly differentiated squamous cell carcinoma was associated with reduced survival rate. Cases with thrombocytosis were associated with poor out come.

According to HeflerL et al & other similar studies thrombocytosis & thrombocytopenia are associated with unfavourable prognosis. [2]

41 (38.31%) cases showed regional lymph node metastasis whereas 8 (7.47%) cases showed distant metastasis which included such as liver, breast & lung. Majority of cases which showed regional & distant metastasis, were poorly differentiated followed by moderate differentiation. The mean platelet count of cases showing lymph node metastasis was in the high count group that is 4.46 lakh/cumm. Those which show distant metastasis had mean platelet count 4.69 lakh/cumm.

Camisasca et. al. had reported 5 year survival rate of oral squamous cell carcinoma to be 92% in patient without recurrence & 30% in patient of recurrence. [18]

Post-operative tumor recurrence leads to high morbidity & mortality. [17] High platelet count & poor tumor differentiation, presence of vascular invasion, regional & distant metastasis are poor prognostic factors in patient of head & neck squamous cell carcinoma.

V. Conclusion

Pre treatment thrombocytosis is an independent prognostic factor in primary head & neck squamous cell carcinoma. High platelet counts showed significant association with poor differentiation as a grade of tumor increases, the rate of recurrence rises, poor grade of differentiation, presence of vascular invasion, regional & distant metastasis are directly proportional to decreased survival, increased morbidity & poor quality of life.

References

[1]. Bagan JV, Scully C. Recent advances in oral oncology 2007: epidemiology, aetiopathogenesis, diagnosis and prognostication. Oral Oncol. 2008;44:103-108.
[2]. Hefler L, Mayerhofer K, Leibman B, Obermair A, Reinthaller A, Kainz C et al. Tumor anemia and thrombocytosis in patients with vulvar cancer.Tumour Biol 2000;21:309-14.
[3]. Symbas NP, Townsend MF, El-Galley R, Keane TE, Graham SD, Petros JA. Poor prognosis associated with thrombocytosis in patients withrenal cell carcinoma. BJU Int 2000;86:203-7.

[4]. Monreal M, Fernandez-Llamazares J, Pinol M, Julian JF, Broggi M, EscolaD et al. Platelet count and survival in patients with colorectal cancer:A preliminary study. Thromb Haemost 1998;79:916-8.

[5]. Wheler J, Tsimberidou AM, Hong D, Naing A, Jackson T, Liu S et al. Survival of patients in a Phase 1 Clinic: The M. D. Anderson CancerCenter experience. Cancer 2009;115:1091-9.

[6]. Jurk K, Kehrel BE. Platelets: physiology and biochemistry. Semin Thromb Hemost 2005, 31:381–392.

[7]. de Gaetano G. Historical overview of the role of platelets in hemostasis and thrombosis. Haematologica 2001, 86:349–356.

[8]. Wakefield LM, Smith DM, Flanders KC, Sporn MB. Latent transforming growth factor-beta from human platelets. A high molecularweight complex containing precursor sequences. J Biol Chem 1988,263:7646–7654.

[9]. Banks RE, Forbes MA, Kinsey SE, Stanley A, Ingham E, Walters Cet al. Release of the angiogenic cytokine vascular endothelial growth factor (VEGF) from platelets: significance for VEGFmeasurements and cancer biology. Br J Cancer 1998, 77(6):956–964.

[10]. Pilatova K, Greplova K, Demlova R, Bencsikova B, Klement GL, Zdrazilova-Dubska L. Role of platelet chemokines, PF-4 and CTAP-III,in cancer biology. J Hematol Oncol 2013, 6:42.

[11]. Senzel L, Gnatenko DV, Bahou WF. The platelet proteome. CurrOpin Hematol 2009, 16:329–333.

[12]. Guo F, Parker Kerrigan BC, Yang D, Hu L, Shmulevich I, Sood AK et al. Post-transcriptional regulatory network of epithelial-tomesenchymaland mesenchymal-to-epithelial transitions. J Hematol Oncol 2014, 7:19.

[13]. Saito Y, Haendeler J, Hojo Y, Yamamoto K, Berk BC. Receptor heterodimerization: essential mechanism for platelet-derived growth factor-induced epidermal growth factor receptor transactivation. Mol Cell Biol 2001, 21:6387–6394.

[14]. Labelle M, Begum S, Hynes RO: Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011, 20:576–590.

[15]. Kaser A, Brandacher G, Steurer W, Kaser S, Offner FA, ZollerH et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. Blood 2001, 98(9):2720–2725.

[16]. Suzuki A, Takahashi T, Nakamura K, Tsuyuoka R, Okuno Y, EnomotoT et al. Thrombocytosis in patients withtumors producing colony-stimulating factor. Blood 1992,80(8):2052–2059.

[17]. Bo Wang, Shu Zhang, Kai Yue and Xu-Dong Wang. The recurrence and survival of oral squamous cellcarcinoma: a report of 275 cases. Chienese Journal of Cancer. 2013 Nov; 32(11):614-618.

[18]. Camisasca DR, Silami MA, Honorato J Dias FL, de Faria PA, Lourenço Sde Q. Oral squamous cell carcinoma clinicopathological features in patients with and without recurrence. ORL J Otorhynological Relat Spec 2011;73:170-176.