Original Article

Architectural changes in the regional lymph nodes of oral squamous cell carcinoma

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Abstract

Background: The lymph nodes (LNs) in oral squamous cell carcinoma (OSCC) are enlarged as a result of reactive lymphadenopathy, metastasis or both. In response to tumor-associated antigens, diverse cell populations of LNs react in different ways, giving rise to a multitude of morphological patterns (MPs). The prognostic value of MPs has been contested. Hence, the aim of the study was to evaluate morphological alterations in the LNs related to LN metastasis (LNM), tumor size, grade and stage and the prognostic value for OSCC.

Materials and Methods: LN sections of 40 OSCCs were evaluated. Six MPs were observed: germinal center predominance (GCP), lymphocyte predominance (LP), sinus histiocytosis (SH), vascular transformation of sinuses (VTS), lymphocyte depleted (LD) and granulomatous reaction (GR). The data were subjected to Chi-square test.

Results: Four-hundred and eighteen nodes were evaluated, of which 24 were metastatic and 394 nonmetastatic. The predominant MP of LN reactivity was of VTS (116 nodes) followed by GCP (105); LP (90), LD (52), SH (43) and GR (12). A significant association was noted between LN status and the MPs. Risk of LNM with LP was less (13%) when compared with GCP (79%). A statistically significant relation was noted between the predominant MP and metastatic and nonmetastatic cases and with the tumor stage.

Conclusion: GCP pattern prevails in metastatic and advanced-stage tumors. LP or VTS/SH is prominent in early-stage tumors and nonmetastatic cases. MPs indicate the immune status and aid in foreseeing susceptibility to LNM, thus serving as a surrogate marker.

Keywords: Morphologic pattern, oral squamous cell carcinoma, regional lymph nodes

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INTRODUCTION

Regional lymph nodes (RLNs) tributary to tumor-bearing organs are considered anatomic barriers to tumor spread. This imitates the host immunologic response. RLNs are also the site where precise immune interactions between tumor antigens and lymphoid cells go on.[1] It has come to recognition that there is certainly an active interrelation between the immunologic abilities of the lymphoid system and malignancy.[2] According

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to these views, the primary antitumor function of LNs is not only filtration but also immunologic tumor surveillance.[1,3]

The RLNs are commonly enlarged as a result of reactive lymphadenopathy, tumor metastasis or both. Enlargement of LNs may be caused by cancer cells or due to reactive hyperplasia of LN in response to tumor-associated antigens (TAAs). In reaction to TAAs, the diverse cell populations of RLNs react in diverse ways, giving rise to a multitude of morphological patterns (MPs).[1] TAAs, shed by tumor cells or released by cell death, in addition to viable tumor cells, are carried by lymph to the draining LNs, providing constant nonspecific and specific stimulation.[2] Morphological evaluation of the RLNs has aided in understanding the immune response (IR).[4,5] Only few studies have investigated the possible correlations between patterns of LN reactivity and prognosis in malignancies.[6] Analysis of MPs in RLNs draining the tumor could reveal the immunological host–tumor association and give details on prognosis and patient survival.[4,6] The prognostic value of the MPs has been contested by some authors.[1] Hence, this study was undertaken to observe the MPs in the cervical LNs of oral squamous cell carcinoma (OSCC) cases and to correlate these patterns with the tumor size, stage and grade and LN metastasis (LNM).

MATERIALS AND METHODS

A cross-sectional study aimed at assessing the relation between MPs and the prognostic value for OSCC was undertaken. The study was carried out after obtaining permission from the Institutional Ethics Committee (IRB. No. 2015/S/OP/45). For the assessment of cervical LNs, sections were obtained from the radical neck dissection specimens of 40 OSCCs reported in the Department of Oral Pathology. Patients who had undergone surgical excision of the lesion along with radical/modified radical neck dissection in the cranio-facial unit of the institution from 2015 to 2017 were included. A consecutive sampling was done.

OSCCs which were treated elsewhere before reporting to institution, patients who were treated only with local resection and patients who were on preoperative chemotherapy or radiotherapy were excluded.

Excised primary lesions along with neck specimens were received and grossed according to the standard protocol. The representative tissue of LNs was processed and 4–6 μ sections were obtained and stained with hematoxylin and eosin. A minimum of three sections were taken from LNs at different levels (Levels I–V) and were evaluated by two independent observers to conclude the predominant MP. To measure the IR in the RLNs, the criteria used were based on a standardized system of reporting human LN morphologic characteristics in relation to immunologic function.[1] The morphologic responses were classified into six types comprising of germinal center predominance (GCP), lymphocyte predominance (LP), sinus histiocytosis (SH), vascular transformation of sinuses (VTS), lymphocyte depleted (LD) and granulomatous reaction (GR) [Figures 1 and 2].

The demographics of the cases, along with size, grade, stage and LN parameters, were recorded. The data were analyzed by IBM SPSS Statistics 20.0 software (IBM Corp., Armonk, NY, USA). The statistical tests were performed using the Pearson's Chi-square test and odds ratio. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Overall, 418 LNs were collected from 40 OSCCs and were examined. It was found that 13 (32.5%) cases showed metastasis and 27 (67.5%) were nonmetastatic. The total number of LNs examined was 418, with a mean of 10.45/case. The number of nodes available for each case selected for the study ranged from 2 to 23. Of 418 LNs, 24 (6%) were positive, which showed the presence of metastatic foci and the remaining 394 (94%) were nonmetastatic.

Of 40 cases, 33 were male and 7 female, with the age range of 30–70 years. Twenty-three cases chiefly involved buccal mucosa and/or gingivobuccal sulcus, six cases in retromolar trigone, six cases in tongue, three cases in lip and two cases in palate. Ten (25%) cases were in Stage I, 15 (37.5%) cases were in Stage II, 8 (22.5%) cases were in Stage III and 6 (15%) cases were in Stage IV.

The predominant pattern of LN reactivity was of VTS (116 nodes) followed by GCP (105), LP (90), LD (52), SH (43) and GR (12) [Table 1]. A statistically significant association was noted between the LN status and the MP [Table 2 and Graphs 1 and 2]. In metastatic nodes, GCP was the predominant pattern. Risk of LNM was higher with GCP (79%) compared with LP (13%). The odds of having metastasis in LN with predominant GCP is 6 times greater (95% CI; 1.82-22.44) ($P = 0.001$) than odds of having metastasis in LN with predominant LP pattern. In nonmetastatic nodes, VTS/SH (40%) pattern dominates.

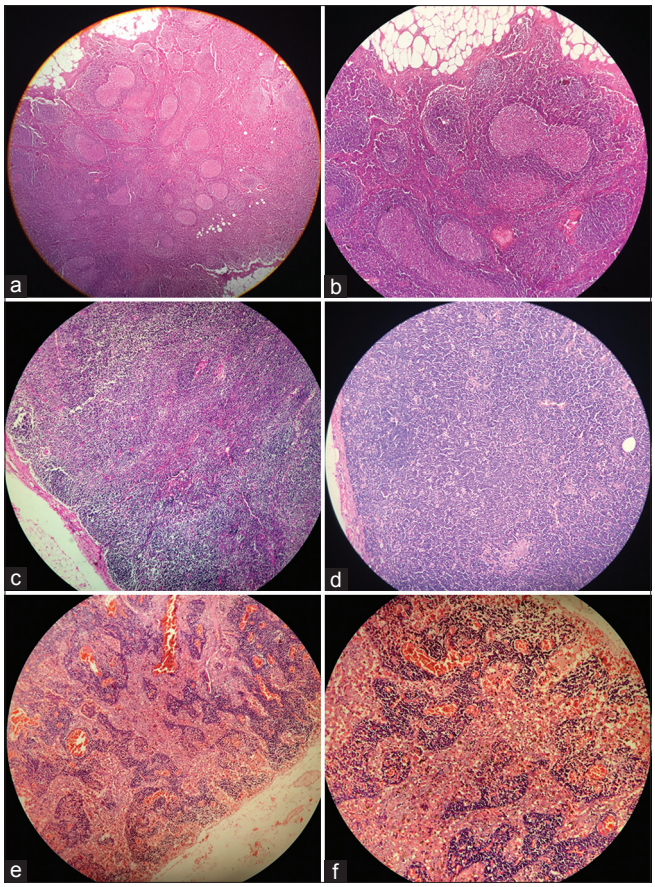


Figure 1: Photomicrographs showing (a and b) germinal center predominance; (c and d) lymphocytic predominance; (e and f) sinus histiocytosis

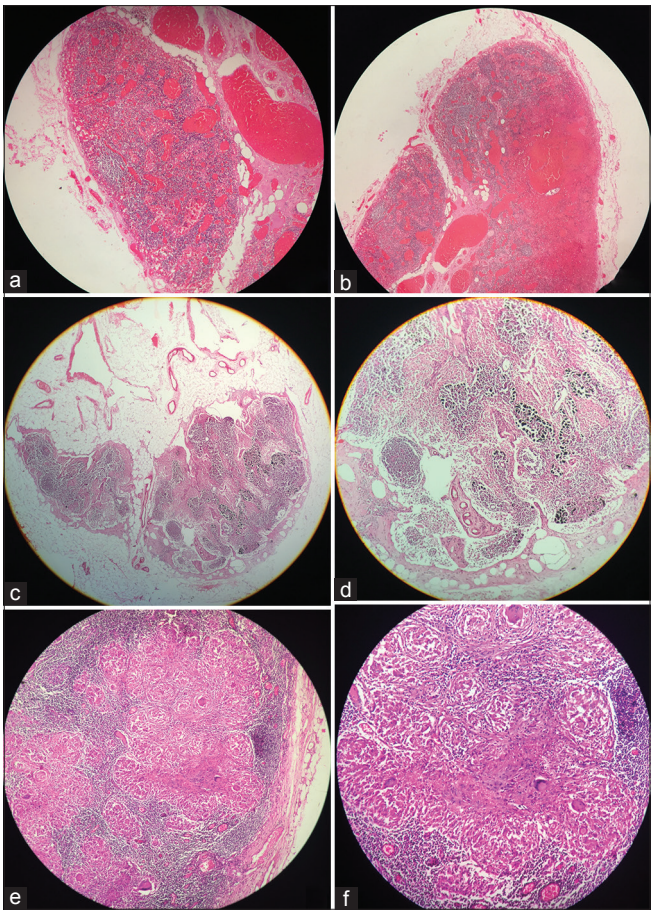


Figure 2: Photomicrographs showing (a and b) vascular transformation of sinus; (c and d) lymphocytic depleted; (e and f) granulomatous reaction

In seven OSCC cases, ten LNs from level IV and V showed LD pattern with lot of pigments, which were most likely to be lipofuscin or ceroid. Twelve LNs from three tongue carcinomas showed caseation necrosis, which were suggestive of tuberculosis.

The metastatic nodes showed three types of patterns: total replacement (2 LNs), metastasis + GCP (19 LNs) and metastasis + LP (3 LNs) [Figure 3].

All the cases were divided into four different groups according to the LN immunoreactivity. Based on the predominant pattern which was noticeable, forty OSCC cases were grouped as follows: GCP (12) (30%), LP (16) (40%), VTS/SH (7) (17.5%) and LD/GR (5) (12.5%) [Table 3].

A significant association was noted between the predominant MP and LNM [Graph 3 and Table 4]. Of 12 cases of dominant GCP pattern, LNM was seen in 10 (83.3%) cases when compared with 2 (16.7%) cases without LNM. This difference was statistically significant ($P < 0.05$) and could deduce that the cases with GCP had higher risk of LNM. Of 16 cases of predominant LP pattern, metastasis was seen in a case (6%) when compared with 15 (94%) cases without metastasis, concluding that cases with an LP had less likelihood of LNM. All seven cases of dominant VTS/SH showed no LNM.

Table 1: Predominant morphological pattern in the lymph node of oral squamous cell carcinoma

Predominant pattern	Number of LNs (%)
GCP	105 (25.00)
LP	90 (21.53)
SH	43 (10.28)
VTS	116 (27.75)
LD	52 (12.44)
GR	12 (2.80)
Total	418 (100)

LNs: Lymph nodes, GCP: Germinal center predominance, LP: Lymphocyte predominance, SH: Sinus histiocytosis, VTS: Vascular transformation of sinuses, LD: Lymphocyte depleted, GR: Granulomatous reaction

Correlating the MPs with the tumor size or grade did not give any significant result ($P = 0.84$) ($P = 0.19$). A significant association was noted between MPs and stage [Table 5]. Eighty percent of Stages I and II (20/25) showed an LP or VTS/SH and 60% (9/15) of Stages III and IV showed

Table 2: Predominant morphological pattern in metastatic and nonmetastatic lymph nodes of oral squamous cell carcinoma

LN status	No LN	GCP (%)	LP (%)	VTS/SH (%)	LD/GR (%)	χ^2	*P*
Metastatic	24	19 (79.20)	3 (12.50)	0 (0)	2 (8.30)	41.068	<0.0001
Nonmetastatic	394	86 (21.80)	87 (22.1)	159 (40.40)	62 (15.70)		
Total	418	105 (25.11)	90 (21.53)	159 (38.03)	64 (15.31)		

LN: Lymph node, GCP: Germinal center predominance, LP: Lymphocyte predominance, VTS/SH: Vascular transformation of sinuses/sinus histiocytosis, LD/GR: Lymphocyte depleted/granulomatous reaction

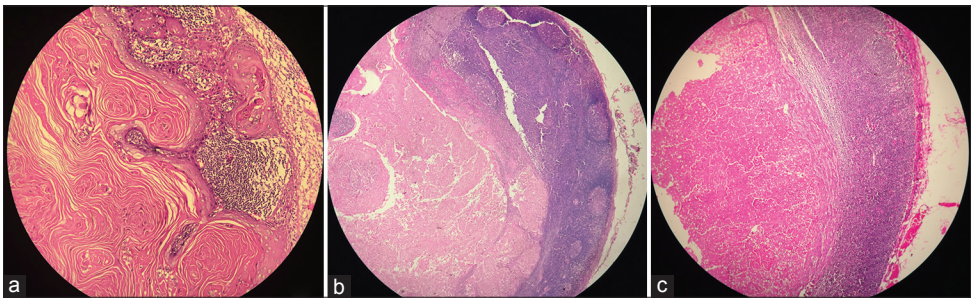
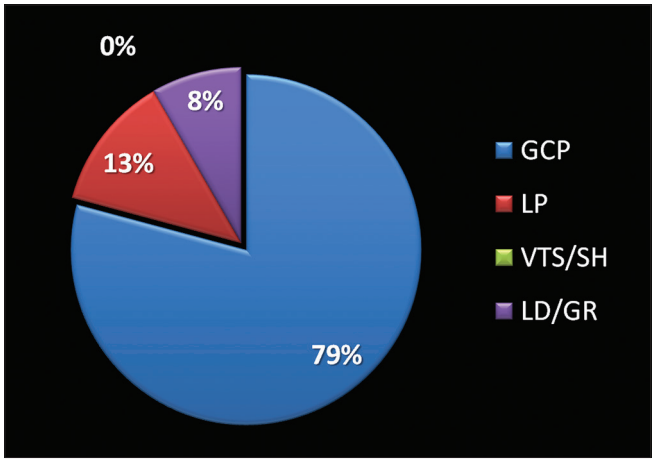
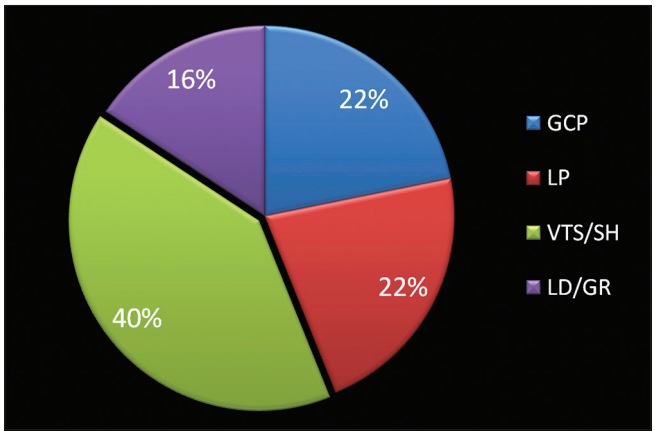


Figure 3: Photomicrographs showing (a) total replacement; (b) metastasis with germinal center predominance; (c) metastasis with lymphocytic predominance



Graph 1: Predominant morphologic pattern in metastatic lymph nodes of oral squamous cell carcinoma



Graph 2: Predominant morphologic pattern in the nonmetastatic lymph nodes of oral squamous cell carcinoma

GCP. LP and VTS/SH patterns dominate in early stage. GCP predominates in the advanced stage.

DISCUSSION

OSCC is the most frequent head-and-neck cancer, accounting for more than 90% of cases.[7] OSCC grows locally and then it spreads to the RLNs. The occurrence of regional LNM in OSCC is relatively high, at 34%–50%.[8,9] LNM is the foremost determinant of the stage and prognosis.[2,10] Neck metastasis has been considered as one of the most important prognostic factors in head-and-neck cancers.[4] The involvement of LNs by metastatic spread signifies the start of a new phase in cancer progression.[2,10]

OSCC is known to be associated with early deficiencies of cell-mediated immunity (CMI), the pathology of which is reflected in the histology of the RLNs. LN morphology does reflect certain parameters of IRs associated with humoral immunity and CMI.[4] Much in advance to the invasion of LN by the tumor, the LN reacts to the numerous molecules produced by and in response to the tumor. The IR can be assessed histologically in the draining LN. Evaluation of the MPs is, thus, a consistent method to assess the host immune status as well as an indicator of the potential of the cancer cells to invade.[5]

Identification of the patterns of LN reactivity to the presence of tumors is vital in the study of surgical specimens. Studies have investigated possible correlations between MPs and prognosis, so far with ambiguous, inconclusive results including colon, stomach, oral, breast, lung, and uterine cervix.[2] The MPs in RLNs have been studied in various types of cancers for prognostic significance, but there are only just few studies in OSCC.[4,7]

A proposal for standardized system of reporting human LN morphology in relation to IR was published in 1973 by the WHO.[1] One of the four major histologic patterns such as LP, GCP, SH and LD may be seen and more often a combinations thereof. In the present investigation, apart from the aforementioned patterns, VTS and GR were also assessed.

In LP pattern, lymphoid follicles are effaced and nonreactive germinal center are inapparent whereas the paracortex is markedly thickened.[1] This pattern was observed in 90 nodes in the present analysis. LP pattern is thought to reflect changes related to CMI and to be associated with a better prognosis.[1,4,11] Increased volume caused by hyperplasia of follicles, prominent germinal centers and enlarged medullary cords are associated with humoral immunity.[1] This GCP pattern was noted in 105 LNs in this study.

SH is characterized by markedly distended sinus spaces and hyperplasia of histiocytes lining these sinuses. Such a pattern was noted in 43 (10%) LNs in this study. Suchitra *et al*. found 21 nodes with SH and 42 nodes with prominent vascularity apart from four basic patterns in 372 LNs.[11] Markedly distended LN sinuses with or without blood and LN architecture being completely replaced by the proliferation of congested vasculature typifies VTS. Such changes were noted in 116 LNs in this study. This is the first report to find and state that the predominant pattern of LN reactivity was of VTS, followed by GCP, LP and others. Even though the task of angiogenesis is uncertain, it is proposed that because of the rich vascularity of LNs, neoangiogenesis is redundant for the growth of metastatic tumor.[12]

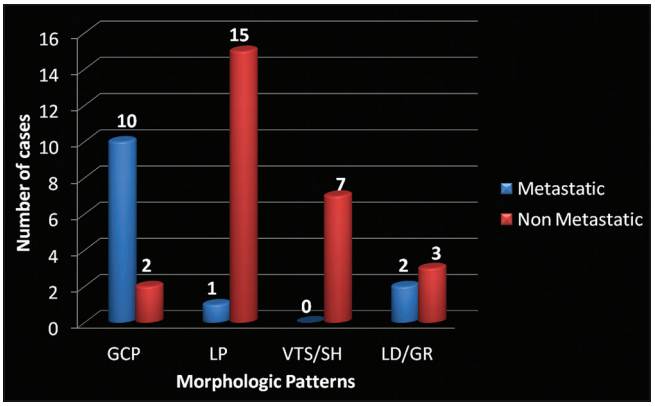
The uncommon unstimulated pattern is frequently observed in levels IV–V, implying that as the levels of nodes are away from primary site, the nodal pattern remains unchanged, suggesting reduced antigenic stimulus.[11] LN is of normal or diminished size, and the lymphocyte population is depleted. Loosely packed lymphocytes are separated by deposits of amorphous substance and areas of fibrocollagen describe LD. These changes reflect an exhausted LN.[1] LD was noted in 52 LNs.

Pigments are a common finding within the cytoplasm of sinusoid macrophages in an LN. The most common

Table 3: Oral squamous cell carcinoma cases categorized according to the predominant lymph node morphological pattern

Predominant pattern	OSCC cases (%)
GCP	12 (30.00)
LP	16 (40.00)
VTS/SH	7 (17.50)
LD/GR	5 (12.5)
Total	40 (100)

OSCC: Oral squamous cell carcinoma, GCP: Germinal center predominance, LP: Lymphocyte predominance, VTS/SH: Vascular transformation of sinuses/sinus histiocytosis, LD/GR: Lymphocyte depleted/granulomatous reaction



Graph 3: Predominant morphologic pattern in metastatic and nonmetastatic oral squamous cell carcinoma cases

Table 4: Association of predominant morphological pattern to metastatic and nonmetastatic cases

Predominant pattern	OSCC cases (*n*)	Metastatic cases (%)	Nonmetastatic cases (%)	χ^2	*P*
GCP	12	10 (83.3)	2 (16.7)	22.659	<0.0001
LP	16	1 (6.2)	15 (93.8)		
VTS/SH	7	0 (0.0)	7 (100.0)		
LD/GR	5	2 (40.00)	3 (60.00)		
Total	40	13 (32.50)	27 (67.50)		

OSCC: Oral squamous cell carcinoma, GCP: Germinal center predominance, LP: Lymphocyte predominance, VTS/SH: Vascular transformation of sinuses/sinus histiocytosis, LD/GR: Lymphocyte depleted/granulomatous reaction

Table 5: Association of predominant morphological pattern to tumor stage in oral squamous cell carcinoma cases

Predominant pattern	OSCC cases (*n*)	Early stage (I and II) (%)	Advanced stage (III and IV) (%)	χ^2	*P*
GCP	12	3 (25.00)	9 (75.00)	14.16	0.003
LP	16	14 (87.50)	2 (12.50)		
VTS/SH	7	6 (85.70)	1 (14.30)		
LD/GR	5	2 (40.00)	3 (60.00)		
Total	40	25 (62.50)	15 (37.50)		

OSCC: Oral squamous cell carcinoma, GCP: Germinal center predominance, LP: Lymphocyte predominance, VTS/SH: Vascular transformation of sinuses/sinus histiocytosis, LD/GR: Lymphocyte depleted/granulomatous reaction

pigments are hemosiderin, ceroid/lipofuscin and melanin. Hemosiderin is an iron-containing golden-brown granular material, and macrophages containing this pigment are found within the medullary cords and sinuses with sinus erythrocytosis. Lipofuscin is a golden-brown, finely granular pigment, but it is derived from the breakdown products of lipids, usually from cell membranes. Ceroid is a variant of lipofuscin. Ten nodes showed brown-black, finely granular pigments. Most of these LNs were showing LD or GR.[13] The pigment noted in these LNs could be either lipofuscin or ceroid which is the product of cell breakdown, representing the exhaustion of IR.

GR in the LN draining cancer is rare. Clusters of epithelioid histiocytes at times resembling granulomas may be seen in draining LNs due to unknown reasons. The main causes for GR at the drainage sites of malignancies may be idiopathic, foreign body reaction to necrotic tumor, therapy-related granulomas, metastasis and associated systemic illnesses such as tuberculosis and sarcoidosis. Subtle morphological features which may be helpful in differentiating a coexisting infection or tumor-induced granuloma need to be addressed. Association of carcinoma with other systemic disease-producing granulomas is rare.[14] In this investigation, 12 nodes from three tongue carcinomas showed the presence of caseating granulomas suggestive of coexisting systemic illness, most likely tuberculosis. In all cases, a search for the acid-fast bacilli was attempted using Ziehl–Neelsen stain for *Mycobacterium bacillus* on LN sections. Red mycobacteria against the pale blue background were noted in only four nodes of two different cases. The bacilli could not be demonstrated in few sections as it was showing burnt-out phase of granuloma with lot of fibrosis and pigments.

LP was noted in 16 OSCC cases. Suchitra *et al*. and Tsakraklides *et al*. found LP as a frequent finding wherein it was suggested that this pattern may be actively engaged in a CMI response.[11,15] Further, it was also suggested that SH and lymphoid hyperplasia are manifestations of CMI and thus may indicate a favorable prognosis.[11,15] In nonmetastatic cases, predominant patterns noted were LP (94%) and VTS/SH (100%), reinforcing the supposition that CMI may avert LN invasion.[4]

On analyzing the LN for the presence or absence of metastasis, it was found that LNM occurred more frequently in patients showing GCP (83%) than in patients with LP pattern (6%), which showed a significant difference. In this investigation, OSCC cases with GCP experienced higher incidence metastasis. The results of this study suggest that these MPs could be useful in determining metastatic potential. Similar results were observed by Tsakradlides *et al*. in uterine cervical and breast cancer,[15,16] Yadav *et al*. in OSCC[4] and Di Giorgio *et al*. in lung carcinoma.[17] In contrast, Berlinger *et al*. in their study on head-and-neck carcinoma found that both GCP and LP patterns experienced fewer incidences of metastasis.[18]

Di Giorgio *et al*. hypothesized that "CMI may prevent LN invasion, whereas, humoral response may facilitate metastases" in patients with lung carcinoma.[17] This hypothesis was supported by Tosi *et al*.[19] and Hunter *et al*.[20] In this investigation, it was found that humoral immunity, as evidenced by GCP, aided nodal invasion, and hence, the aforesaid assumption may perhaps be relevant to OSCC. The appearance of a humoral IR seems to favor the metastatic spread through LNs by block or inhibition of the histiocytes and T-lymphocyte cytotoxic activity against tumor cells.[4]

Investigations done by Tosi et al., Di Giorgio *et al*., Yadav et al., found predominant pattern GCP in higher percentage of metastatic nodes of bronchogenic carcinoma,[19] lung carcinoma[17] and OSCC[4] respectively. In this study, we scrutinized the positive nodes at all levels and found three types of reaction patterns: total replacement 8%, GCP 79% and LP 13%. These findings confirmed the fact that germinal center hyperplasia was associated with LN invasion.[4]

Di Giorgio *et al*. found that lung carcinomas >4 cm have a brisk humoral response, whereas most cases with smaller lesions had poorly developed cortical areas and germinal centers. Progressive growth of primary tumor leads to necrosis, worsening of anaplasia and cytolysis, with shedding of high quantities of TAAs, which are capable of stimulating humoral activity and blocking the cytotoxic action of T cells and thus improving malignant spread.[17] In this investigation, a significant association was observed between the MPs and stage. However, Yadav *et al*. and Raj *et al*. observed no significant relation between the MPs and stage.[4]

CONCLUSION

The results confirm that the MPs of RLNs can be a pointer of the immunologic reactivity in that node. The evaluation of LN reactivity intends to ultimately determine the host IR facing a malignancy. Reactivity patterns indicate the immune status of the OSCC and also help us predict the susceptibility to LNM. GCP pattern prevails in metastatic cases and advanced-stage tumors. In metastatic nodes, GCP pattern dominates than others. In nonmetastatic nodes,

VTS or SH dominates. LP or VTS/SH is prominent in early-stage tumors and nonmetastatic cases. Thus, MPs could be a surrogate marker in predicting LNM. Hence, MPs can assist in forecasting the prognosis. More extensive studies on MPs will be helpful in providing information on patient prognosis and survival. It is apt to state that the MPs of the sentinel node draining the site of the OSCC might be the best prognosticator. It is sensible to take into consideration the immunomorphological aspects while reporting.

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Conflicts of interest

There are no conflicts of interest.

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