Original Article

Importance of histomorphological assessment of regional lymph nodes draining colorectal carcinomas

Reena Mary Ninan[1], Prema Saldanha[2*], Hassan Sona Rai[3]

[1,3]Resident, [2]Professor, Department of Pathology, Yenepoya Medical College, Deralakatte, Mangalore – 575018, Karnataka, INDIA.
Email: premasaldanha@yahoo.co.in

Abstract

Lymph nodes draining tumour are considered anatomic barriers to tumour spread. The involvement of lymph nodes by metastatic spread of tumours signifies the start of a new phase in the progress of a cancer. Lymph node status is one of the most important indicators of clinical outcome. Lymph nodes are also the site where specific immune interactions between tumour antigens and lymphoid cells take place. Enlargement of nodes may be caused by spread of cancer cells or due to reactive hyperplasia of lymph nodes in response to tumour-associated antigens. The various lymphoid cell populations react in various ways, giving rise to different morphologic patterns. The current study is carried out to observe the morphological changes occurring in the regional lymph nodes and to evaluate whether these features could be helpful in assessing the immunological status of the patient and thereby, the prognosis of the patient. In this study, it was found that lymph node reaction pattern and percentage of lymph node replacement by metastatic tumour in positive lymph nodes, as well as the tumour size and reaction pattern in negative lymph nodes and the reaction pattern in negative lymph nodes and MLN ratio showed an association that was found to be statistically significant. More extensive studies on lymph node immune response patterns will be helpful in providing information on patient prognosis.

Key words: carcinoma, colorectal, lymph nodes, reactive.

[*]**Address for Correspondence:**
Dr. Prema Saldanha, Professor, Department of Pathology, Yenepoya Medical College, Deralakatte, Mangalore – 575018, Karnataka, INDIA.
Email: premasaldanha@yahoo.co.in

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INTRODUCTION

The role of the host response to neoplasm has been recognised and for many years the regional lymph nodes in the tumour bearing host has been considered as a barrier to the dissemination of tumour cells. Morphological evaluation of regional lymph nodes has aided in understanding the immune response. Only a few studies have investigated the possible correlations between the patterns of lymph node reactivity and prognosis in malignant tumours. The present prospective study is conducted to observe the architectural changes occurring in the regional lymph nodes with metastasis and those without metastasis. It is assumed that the histological analysis of the regional tumour draining lymph nodes could elucidate the immunological host tumour relationship and render additional information on patient survival.[1]

MATERIALS AND METHODS

This prospective study was done on resected specimens of cases with carcinoma of the colon and rectum. The specimens were sent in 10% formalin, processed and paraffin embedded. The five micron thin sections were stained with Haematoxylin and Eosin. All the regional lymph nodes isolated were studied. The lymph nodes were divided into two groups, those with metastasis and those without metastasis. The morphological patterns of the immune responses were classified according to the WHO proposal.[2]

The morphological patterns were correlated with the presence or absence of metastasis,and the characteristics of the primary tumour.

OBSERVATIONS AND RESULTS

In the present study there were 23 cases of colorectal carcinoma and a total of 198 lymph nodes were

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examined. The age of the patients ranged from 20 to 79 years, with the maximum number of cases (10) in the age group 40 -59 years, followed by 8 cases in the range 60-79 years, and 5 cases in the range 20-39 years. Of the 23 cases of colorectal carcinoma studied, in 15 cases the tumour measured greater than or equal to 4.5 cms andin 8 cases the tumour measured less than 4.5cms. In the present study, out of the 15 cases of large sized tumours, 2 cases were N2 (>4 lymph nodes with metastatic tumour), 5 cases were N1 (1-3 lymph nodes with metastatic tumour), and 8 cases had no lymph node metastasis. Out of 8 cases of small sized tumours, 3 cases were N2, 2 cases were N1 and 3 cases had no lymph node metastasis. The comparison of the tumour size and the regional lymph node positivity was not statistically significant (p= 0.408). Out of the 15 cases of large sized tumours, 2 cases had MLN (metastatic lymph node) ratio, ratio of 1 and 8 cases had MLN ratio of 0. Out of the 8 cases of small sized tumours, 2 cases had MLN ratio of 1 and 3 cases had MLN ratio of 0. The chi-square test showed no statistical significance (p= 0.0409). Most of the cases (14 cases = 61%) were well differentiated adenocarcinoma. There were 8 cases of moderately differentiated and only one case of poorly differentiated adenocarcinoma.The comparison of the size of the tumour and the microscopic grade showed no association (p =0 .343). In the present study, out of the 8 cases of moderately differentiated, 1 case was N2, 3 cases were N1 and 4 cases had no lymph node metastasis. One case of poorly differentiated carcinoma was N2. Out of the 14 cases lymph node of well differentiated 7 cases had no lymphnode metastasis, 4 cases were N1, and 3 cases were N2. The findings were not statistically significant (p= 0.309). In the present study, out of 7 cases of moderately differentiated 2 cases had MLN ratio 1 and 4 cases had 0.1 case of poorly differentiated adenocarcinoma had MLN ratio1.Out of 15 cases of well differentiated, 7 cases had MLN ratio 0 and 1 case had 1 value.The comparison of tumour grade and MLN ratio was not statistically significant (p=0.678).

The depth of tumour invasion in the cases of adenocarcinoma colon was as follows:

pT1- invasion into submucosa – 2 cases, pT2 – invasion into muscularis propria - 7 cases, pT3- invasion through the muscularis propria into subserosa – 4 cases, and pT4 – invasion into other organs/through the visceral peritoneum - 10 cases.Comparison between size of the tumour and the depth of invasion was found to be statistically significant (p = 0.034).

A total of 51 lymph nodes with metastatic tumour were examined. No reaction pattern was recorded in lymph nodes with >90% involvement by metastatic tumour. Tumour size and pattern of reaction in the lymph nodes showing metastasis were correlated. There was no statistical significance (p = 0.066).Comparison of lymph node pattern and percentage of lymph node replacement by metastatic tumour was found to be statistically significant (p = 0.000).

Lymph nodes without metastatic tumour examined were 147. Out of 102 lymph nodes in the large-sized tumours,32 cases had GC (germinal centre predominant) pattern,9 cases had GC+LP (lymphocyte predominant) pattern,14 cases had GC+SH (sinus histiocytosis),17 cases had GC+VT (vascular transformation),1 case had LD (lymphocyte depletion),15 cases had LP,2 cases had LP+SH,6 cases had LP+VT,2 cases had SH pattern and 4 cases had VT pattern.Out of 45 lymph nodes in the small-sized tumours,6 cases had GC pattern,12 cases had GC+LP,9 cases had GC+SH,2 cases had GC+VT,15 cases had LP,1 case had LP+SH.

The comparison between tumour size and tumour reaction pattern showed an association (p=0.002).The comparison of tumour pattern and lymph node involvement was not statistically significant (p= 0.082).The comparison of tumour pattern and MLN ratio showed an association between reaction pattern and MLN (p=0.000).

In the present study it was found that lymph node reaction pattern and percentage of lymph node replacement by metastatic tumour in positive lymph nodes, the tumour size and reaction pattern in negative lymph nodes and reaction pattern in negative lymph nodes and MLN ratio showed an association that was found to be statistically significant. Comparison between size of the tumour and the depth of invasion was also found to be statistically significant

DISCUSSION

Carcinomas spread predominantly by the lymphatic route. Lymph nodes draining a primary tumour are considered act as barriers to the spread of the malignancy. They are also the site where specific immunological interactions between tumour antigens and reacting lymphoid cells take place. The primary antitumour function of lymph nodes is not only filtration but also immunologic tumour surveillance.[3,4]

The involvement of lymph nodes by metastatic spread of tumours signifies the beginning of tumour metastasis. This process indicates that through a succession of molecular changes, these cancer cells have acquired phenotypes that enable them to invade, colonize, and disseminate. Lymph node status is a very important predictor of clinical outcome [5] . Lymph nodes are also the site where specific immune interactions between the tumour antigens and the lymphoid cells take place. Enlargement of nodes may be caused by spread of cancer cells to the lymph nodes or due to reactive hyperplasia of

lymph nodes in response to tumour-associated antigens. The various lymphoid cell populations react in various ways, giving rise to different morphologic patterns.[1]

The major cause of the morbidity and mortality associated with tumours is metastasis. Tumour cells spread by lymphatics to lymph nodes and disseminate the disease. Metastatic tumour cells first appear in the marginal (subcapsular) sinus, from which they penetrate the medullary sinuses, medulla, and cortex; the eventual result may be total parenchymal replacement. Even before metastatic tumour cells are present in the lymph node, reactive changes take place which reorganize favourably the microenvironment.[5,6]

Cancer management and prognosis depend to a great extent on the presence and degree of tumour metastasis. These are evaluated by staging tumours according to the internationally accepted tumour-node-metastasis (TNM) system. Of all the various criteria used as prognostic factors, the most powerful remains the description of anatomic spread according to the TNM staging. This classification by stage is as follows: stage 0, preinvasive neoplasia; stage I, tumour confined to the organ of origin; stage II, direct tumour spread outside the organ of origin; stage III, metastasis to regional lymph nodes; and stage IV, metastasis to distant sites. Each successive stage in the TNM system indicates a significant decrement in the prognosis. The diagnosis of lymph node tumour metastasis is therefore essentially important for cancer therapy. This consists not only of establishing the presence of lymph node metastasis but also of evaluating the site of the primary tumour and its degree of histologic differentiation and determining the tumour cell phenotype and prognostic indicators of tumour cell behaviour.[5]

Over the past few years, the ratio of metastatic to examined lymph node (MLNR) has been studied widely. Nearly all researchers demonstrated that the MLNR is an independent prognostic factor that is highly related to the survival of patients with colon cancer and it has been recommend that the MLNR should be applied in prognostic assessment.[7,8,9] Lymph nodes play an essential role in the control of tumour progression. In response to the antigenicity of tumour cells, regional lymph nodes may initiate and develop complex immune reactions. At the same time, they may entrap circulating tumour cells that have originated in their tributary territories. Acting as efficient barriers, the lymph nodes may be able to destroy invading tumour cells completely, or at least stop their dissemination temporarily. Lymph node metastasis, in contrast to the vascular spread of tumours, presents an opportunity, even if temporary, for surgical intervention. In addition, because of their accessibility, lymph nodes with metastatic tumour present the best opportunity for primary tumour diagnosis through biopsy and histologic evaluation.[5]

In response to tumour-associated antigens, the various cell populations of regional lymph nodes react in different ways, giving rise to a multitude of morphologic patterns.The term tumour-reactive lymphadenopathy is used which is defined as reactive, enlarged, regional lymph nodes draining tumours.[1]

A few studies have been devoted to the analysis of such reactions, in an effort to understand the mechanisms of lymph node metastases. Some studies have correlated various histologic patterns of reactive lymph nodes with the dissemination of tumours in cancers of various organs.[1]

Tumour-associated antigens, shed by tumour cells or released by cell death, in addition to viable tumour cells, are carried by lymph to the draining lymph nodes, providing constant nonspecific and specific stimulation. Thus, various defence reactions may be triggered, including phagocytosis, production of antibodies, and sensitization of lymphocytes. Such reactions were investigated in various studies by determining the amounts and types of immunoglobulins in pericancerous lymph nodes and by immunohistochemically detecting epitopes of tumour-associated glycoproteins in the draining lymph nodes.[10]

Sinus macrophages, lymphatic endothelial cells, and follicular dendritic cells in the unaffected lymph nodes show immune reactions with monoclonal antibodies against epitopes of some tumour- or colon-associated glycoproteins that are similar to their reaction to the carcinoma cells of the colonic tumour.[1]

In many cases, markedly enlarged and firm lymph nodes removed as part of radical tumour excision reveal no tumour metastasis on microscopic examination. The morphologic changes of lymph nodes draining tumour-bearing organs provide evidence for antitumour immune reactivity. Recognition of the histologic patterns of lymph node reactivity to the presence of tumours is an important objective in the study of biopsy and surgical specimens [1] . A number of studies have investigated possible correlations between patterns of lymph node reactivity and prognosis, so far without firm, conclusive results including colon,[11,12,13,14,15] stomach[16], oral,[17,18] breast[19,20] lung[21,22] and the uterine cervix.[23] Reactive lymph node hyperplasia is the enlargement of lymph nodes or other lymphoid tissue as a result of stimulation of the lymphoid cells by a variety of antigens. It is a benign, reversible process. The immune responses in lymph nodes may be predominantly of B-cell type, characterized morphologically by either follicular hyperplasia or plasmacytosis, or predominantly of T-cell type, with a characteristic pattern of T-cell hyperplasia.[24,25]

Lymphadenopathies tend to exhibit one of the four characteristic histologic patterns including follicular, sinusoidal, diffuse, or mixed. These patterns represent expansions of the normal follicular, paracortical, medullary, and sinusoidal lymph node compartments. The histologic patterns vary with the etiologic agent, the age of the lesion, as well as with the immune competence status of the host. Therefore, combined or mixed overlapping architectural features are a more common finding than clearly defined histologic patterns on biopsy specimens of lymph nodes without metastasis.[26] A proposal for a standardized system of reporting human lymph node morphology in relation to immune reaction was published in 1973 by the World Health Organization. The authors recommended a topographic examination of the lymph node sections with separate descriptions of the functional areas: cortex with follicles and germinal centres, paracortex, sinuses, and medullary cords. Studies of regional lymph nodes in tumours of various organs show histologic patterns of reactions, possibly with prognostic implications One of four major histologic patterns maybe seen, and more often combinations thereof. The four major patterns include Lymphocyte Predominance, Germinal Centre Predominance, Sinus Histiocytosis and Lymphocyte Depletion. Vascular transformation of lymph node sinuses (VTS) is characterized by conversion of nodal sinuses into capillary-like channels, often accompanied by fibrosis and a Granulomatous Reaction have been described rarely.[1,2] In lymphocyte-predominant tumour-reactive lymphadenopathy, lymph nodes are enlarged particularly because of the increased number of lymphocytes in the paracortical areas (T-cell zone). The lymphoid follicles are effaced, and the nonreactive germinal centres are mostly inapparent, whereas the paracortex is markedly thickened. Such lymphoid hyperplasia may or may not be associated with sinus histiocytosis. The pattern is thought to reflect changes related to cellular immunity and to be associated with an earlier diagnosis and a better prognosis.[1,11,12,13,14,15,19,20,21,22,23]

In germinal centre–predominant tumour-reactive lymphadenopathy, the lymph nodes are enlarged, but the increase in volume is caused by hyperplasia of follicles, particularly the germinal centres which is the B-cell zone. Reactive follicular hyperplasia is the B-cell response to various antigens. A predominantly B-cell response is characterized by hyperplasia of germinal centres and therefore by a follicular pattern [1,2] .Sinus histiocytosis may coexist with these changes, which are considered to be associated with humoral immunity follicles and germinal centres reactive in a tumour-free lymph node may remain reactive in lymph nodes largely replaced by metastatic tumour.[1]

The lymph node follicles become numerous and enlarged , located not only in one row in the cortex but also in two or three rows in the paracortex, corticomedullary junction, and sometimes even the medulla [2] .They vary considerably in size and shape, occasionally coalesce, and display dumbbell, hourglass, or other bizarre configurations. The mantle zone and germinal centre are sharply demarcated in a reactive follicle.[24]

Sinus histiocytosis is associated with a more favourable prognosis. A predominance of sinuses characterizes the morphologic pattern of sinus histiocytosis, which can occur in isolation or together with one of the preceding patterns. The lymph node is enlarged by markedly distended sinuses and hyperplasia of the sinus histiocytes. The pale staining of histiocytes and endothelial cells that line the branching lumina contrasts strongly with the dark staining of lymphocytic areas and produces the characteristic appearance of sinus histiocytosis.[1,2] In lymphocyte depletion, the lymph node is of normal or diminished size, and the lymphocytic population is depleted. The loosely packed lymphocytes are separated by deposits of amorphous substance and areas of fibrocollagen. The vessels have thick walls, with hyaline deposits. Diffuse fibrosis and patchy deposition of hyaline involve both the cortex and medulla. These changes are considered to reflect an exhausted ("burnt out") lymph node and to be associated with metastases and a poor prognosis.[1,2,19,20,21,22,23] Pattern of lymph node reaction has shown that patients with colorectal carcinoma in whom the regional lymph nodes show morphologic evidence of a cell-mediated immune response (manifested by an increased number of paracortical immunoblasts and/or sinus histiocytosis) survive longer than those patients whose nodes do not show these changes.[11,12,13,14,15] The best five-year survivals were seen in patients whose lymph nodes demonstrated immunologic responses in the form of a lymphocyte predominance pattern and, to a lesser degree, the germinal centre predominance pattern. Patients whose lymph nodes demonstrated no morphologic evidence of an active immunologic response, in the form of an unstimulated pattern, or patients whose lymph nodes showed the lymphocyte depletion pattern had the poorest five year survival rate. Further analysis of our results shows that the lymphocyte predominance pattern was found to be more common in nonmetastatic cases and in carcinomas of a high grade of differentiation. Also, it is interesting that the survival rate in cases with lymphocyte predominance pattern and in cases with metastases to the regional lymph nodes was higher.[27] Lymph nodes with combined B- and T-cell hyperplasia were significantly more common in cases of good tumour differentiation. The findings suggest that sinus histiocytosis and

hyperplasia of both major lymphocyte populations are morphological expressions of in vitro antitumour immunoreactivity in the regional lymph node.[13]
Histologic parameters which are thought to reflect either cell-mediated (T cell) or humoral (B cell) immune responses in lymph nodes have been studied in regional lymph nodes. Patients whose lymph nodes show morphological evidence of cell-mediated immunity, manifested either by an increased number of paracortical immunoblasts or sinus histiocytosis, survive significantly longer than those whose lymph nodes show no such changes. Patients whose lymph nodes show simultaneous paracortical activity and sinus histiocytosis have the best survival of all. Histologic parameters which suggest an antibody-mediated immune response (germinal centre activity) were not an important prognostic indicator.[11]

CONCLUSION

Several parameters are used for predicting the prognosis in cancer patients. It is assumed that the histological analysis of the patterns in the regional lymph nodes draining the tumour could elucidate the immunological host-tumour relationship and provide additional information on patient survival. Increasing size of the cancer, higher grade and stage of the malignancy are likely to show decreased number of reactive lymph nodes. It has been found that certain patterns like lymphocyte predominance have a lower risk of metastasis while in some studies germinal centre predominance has a higher risk of metastasis.
In the current study, it was found that lymph node reaction pattern and percentage of lymph node replacement by metastatic tumour in positive lymph nodes was significant. The tumour size as well as MLN ratio and reaction pattern in negative lymph nodes showed an association that was found to be statistically significant. This study is however limited by the small number of cases. More extensive studies on lymph node immune response patterns will be helpful in providing information on patient prognosis.

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