Review Article

Indian Journal of Pathology: Research and Practice
Volume 12 Number 3, July - September 2023
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.12323.2

Benign Epithelial Inclusions in Lymph Nodes: A Diagnostic Challenge for the Pathologists

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How to cite this article:
Mukta Pujani, Cherry Bansal, Meenu Pujani/Benign Epithelial Inclusions in Lymph Nodes: A Diagnostic Challenge for the Pathologists/Indian Journal of Pathology: Research and Practice 2023;12(3) 95–103.

Abstract

Benign inclusions are defined as foci of non neoplastic ectopic tissues in lymph nodes encompassing various types of tissues. Benign epithelial inclusions have been reported in lymph nodes of various anatomical locations including head and neck, mediastinum, axilla, peritoneal, pelvic and inguinal regions. Epithelial inclusions can be divided into epithelial, nevomelanocytic and decidual. Further subtypes based on the tissue of origin include salivary gland tissue, thyroid tissue, squamous epithelial cells, breast tissue, mesothelial cells etc. The nature of tissue in heterotopic inclusions varies according to the location of the lymph nodes. The accurate diagnosis of these benign epithelial inclusions is of utmost clinical importance to prevent misinterpretation of this entity as malignant and hence save the patient from overzealous and inappropriate treatment. Hence, great importance should be given to detailed morphological evaluation of lymph nodes with epithelial inclusions in reaching at an accurate diagnosis. The cytological criteria favouring benign epithelial inclusions over metastatic carcinoma include a lack of significant nuclear atypia, pleomorphism and hyperchromasia. It is very important to create awareness of this rare entity among pathologists to prevent misdiagnosis or overdiagnosis of a malignant lesion.

Keywords: Benign epithelial inclusions; Metastasis; Ectopic tissue; Lymph nodes.

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Received on: 29.09.2023

Accepted on: 02.11.2023

INTRODUCTION

Benign epithelial inclusions are clusters of benign well differentiated epithelial cells in lymph nodes.[1] Benign inclusions are defined as foci of non neoplastic ectopic tissues in lymph nodes encompassing various types of tissues. Benign epithelial inclusions have been reported in lymph nodes of various anatomical locations including head and neck, mediastinum, axilla, peritoneal, pelvic and inguinal regions.[2]

The most important and worrisome feature of these benign inclusions in lymph nodes is their misinterpretation as tumor metastasis. The awareness of the occurrence of such an entity is extremely significant in preventing the over diagnosis of a malignant lesion.

History

The occurrence of benign inclusions in lymph nodes were first brought to attention by Ries *et al* in 1897. Initially, these were observed in lymph nodes from patients with malignant tumors by several authors.[3-6]

Reich *et al*[6] reported the presence of epithelial cells as tubular structures mimicking cysts in the lymph nodes of patients with malignancies of uterus, cervix and vulva. Wertheim *et al*[4] observed benign inclusions in pelvic lymph nodes in 13% of patients who underwent radical hysterectomy with pelvic lymphadenectomies. They interpreted that these were a result of neoplastic disease. Subsequently, it was documented that benign inclusions are also found in lymph nodes of patients without any evidence of malignancy.[3] Moreover, benign inclusions have now been reported in lymph nodes from every location in the body including cervical, axillary, mediastinal, iliac, mesenteric, pelvic etc.

Classification

Inclusions in lymph nodes have been classified by Brooks *et al*[7] in 1990 into three different types depending upon their nature: epithelial, nevomelanocytic and decidual.

Epithelial inclusions can be further subdivided into a variety of types based on the tissue of origin, namely, salivary gland tissue, thyroid tissue, squamous epithelial cells, breast tissue, mesothelial cells. The nature of tissue in heterotopic inclusions varies according to the location of the lymph nodes (Table 1). Salivary gland tissue, thyroid tissue and squamous epithelium are typically encountered in cervical lymph nodes while breast tissue and nevus cell aggregates are commonly observed in axillary lymph nodes. Pelvic lymph nodes often display decidual tissue and epithelium of paramesonephricus types in such inclusions while mesenteric lymph nodes commonly show intestinal glands and mesothelial cells.[3,8]

Fellagra *et al*[9] analysed 18 cases of epithelial inclusions in axillary lymph nodes and classified nodal epithelial inclusions into three categories: glandular type which is the most frequent; squamous type inclusions (least common) and mixed glandular squamous inclusions. The epithelial cells in these inclusions can be observed either as nests, tubular structures resembling glands or they may be present as cysts lined by epithelial cells.

Significance

The accurate diagnosis of these benign epithelial inclusions is of utmost clinical importance to prevent misinterpretation of this entity as malignant and hence save the patient from overzealous and inappropriate treatment. Hence, great importance should be given to detailed morphological evaluation of lymph nodes with epithelial inclusions in reaching at an accurate diagnosis.

Certain criteria have been documented by Khier *et al*[10] (1981) which help in differentiating benign epithelial inclusions from metastatic foci in lymph nodes. Benign inclusions are usually distributed around the lymphoid follicles while metastatic deposits from carcinoma, unless extensive are commonly found near subcapsular sinus. Inclusions may have pseudostratified epithelium while metastatic foci usually have a number of cell layers. The cytological criteria favouring benign epithelial inclusions over metastatic carcinoma include a lack of significant nuclear atypia, pleomorphism and hyperchromasia (Fig. 1, 2).

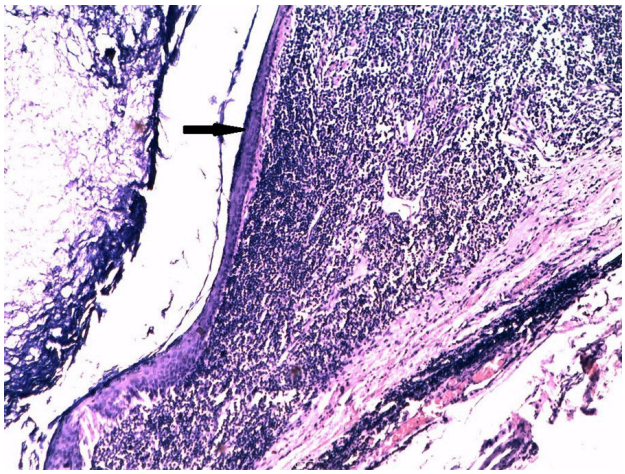

Fig. 1: Photomicrograph showing cyst within the lymph node lined by keratinizing stratified squamous epithelium (black arrow) filled with keratinous debris. The lining shows a lack of significant nuclear atypia, pleomorphism or hyperchromasia. (Hematoxylin & Eosin, 400X)

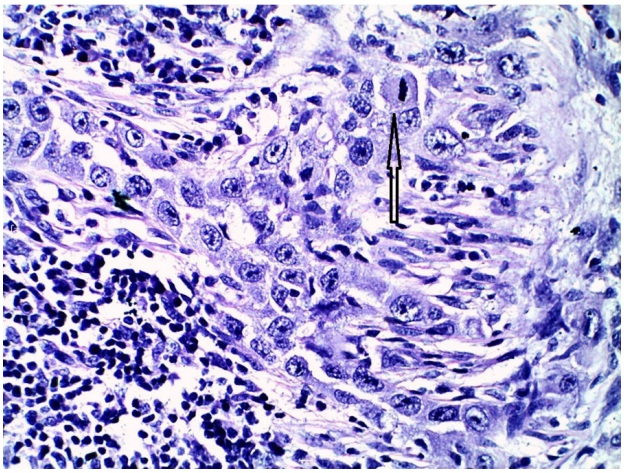

Fig. 2: Photomicrograph showing metastatic deposits from squamous cell carcinoma in a lymph node. Note the atypical cells with marked nuclear pleomorphism, mitosis (arrow). (Hematoxylin & Eosin, 400X)

Origin

The origin of epithelial inclusions remains controversial. Various theories have been proposed to account for the presence of epithelial inclusions in the lymph nodes. First among these is the theory of embryogenesis which explains the origin of these epithelial cells from the entrapment of epithelial cells in the hilum of lymph nodes. Secondly, iatrogenic implantation of epithelial tissues can account for the occurence of benign inclusions in lymph nodes in patients with a prior history of a surgical procedure. Thirdly, a metaplastic theory has been advocated. Lastly, possible origin from transportation of detached epithelial cells as a kind of benign metastasis has also been proposed. The presence of epithelial cells in lymph nodes is usually due to metastasis from a carcinoma. However, less commonly benign epithelial cells may be found in lymph nodes without any relation to malignancy.[1,3]

Epithelial inclusions of lymph nodes of various locations present different problems of pathogenesis and differential diagnosis. Hence, we shall discuss the various types of inclusions found in lymph nodes from different sites separately.

Cervical lymph nodes

Benign epithelial inclusions most frequently observed in cervical lymph nodes include salivary gland tissue and thyroid tissue. Salivary gland acini and ducts are usually found in the upper cervical lymph nodes (Fig. 3) and are thought to be aberrant or parotid gland tissue.[1] Infact, ectopic parotid has often been observed in intraparotid lymph nodes in parotidectomies performed for other lesions. According to Marques *et al*[11], these inclusions arise by progressive development of a lymph node in salivary lobules. So, these salivary inclusions must not be qualified as ectopic.

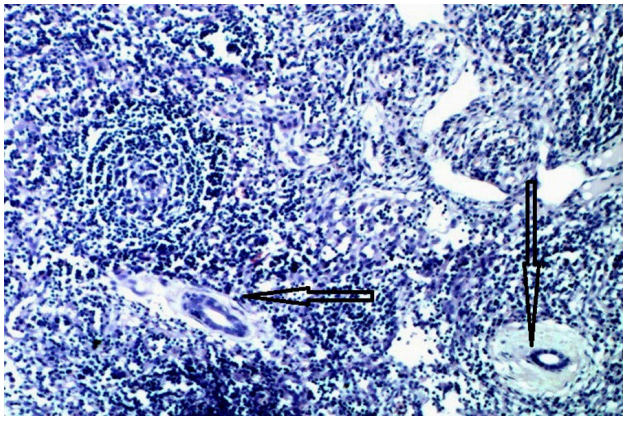

Fig. 3: Photomicrograph showing salivary duct inclusions (arrow) within a lymph node. (Hematoxylin & Eosin, 400X)

Daniel[12] reviewed salivary tumors arising from heterotopic salivary inclusions in the periparotid and cervical lymph nodes over a period of 25 years and found 24 such cases. Out of these, 9 patients had benign salivary inclusions in lymph nodes while 15 patients developed salivary tumors arising from heterotopic salivary tissue in lymph nodes. The most common tumor to develop in these salivary inclusions was found to be warthin's tumor (8/15 cases). Manganaris *et al*[13] also reported 4 cases of salivary tumors arising from salivary inclusions, out of which 3 were warthin's tumor.

Histogenesis of Warthin tumor (WT) is debatable. According to a predominant theory, it is thought to arise from heterotopic salivary ductal inclusions in parotid lymph nodes. To test this hypothesis, Cope *et al*[14] compared the prevalence of salivary inclusions in parotid LN between patients diagnosed with warthin's tumor and pleomorphic adenoma (PA) (46 vs 52 patients). 71.7% of WT and 32.7% of PA had inclusions in any LN. The presence of inclusion was a significant predictor for WT versus PA ($p = 0.019$). Salivary inclusions were more frequent in parotid LN from patients with WT than PA. Their results supported the hypothesis that WT arises from salivary inclusions in lymph nodes.

Thyroid tissue has occasionally been observed microscopically in the lower cervical lymph nodes incidentally in radical neck dissections performed for head and neck malignancies. The clinical significance of incidentally detected thyroid tissue in cervical nodes is controversial as to whether these represent benign inclusions or metastatic foci from thyroid cancers. The treatment protocol in such cases is not well documented as these occur in

the setting of another malignancy.

Butler *et al*[15] reported thyroid malignancy in 72% (16/22) patients with thyroid tissue inclusions in cervical lymph nodes. They suggested that the benign histological appearance and lack of a papillary component doesn't rule out primary thyroid carcinoma. In most of their cases, the primary thyroid carcinoma was detected only after extensive sectioning. Kr *et al*[16] also reviewed 1602 neck dissections in patients with head and neck cancers and encountered 5 patients with incidental thyroid tissue with features of malignancy in cervical nodes. In four of these cases, subsequent thyroidectomies revealed primary thyroid cancers. They emphasized that a thorough sampling and screening of lymph nodes by the pathologist is essential.

Yamamoto *et al*[17] found 3 cases of incidental papillary thyroid carcinoma (PTC) in cervical lymph nodes of patients with oral cancers. They proposed the possibility that thyroid carcinoma in cervical node is not always metastatic, but may arise occasionally from heterotopic thyroid tissue. Resta *et al*[18] reported 8 cases with incidental metastases of well differentiated thyroid carcinoma in lymph nodes of patients with head and neck squamous cell carcinomas. Only one patient revealed a minimal focus of PTC on thyroidectomy. The choice of treatment for such patients with a coexistent neoplasm (with poor prognosis) is difficult, the options that exist include radical thyroidectomy. However, the prognosis of the patient is determined by the more aggressive squamous cell carcinoma. They stressed upon the importance of an accurate reevaluation and follow up of patients with incidental occult metastasis for detection of a primary thyroid tumor. Fliegelman *et al*[19] identified five patients with incidental thyroid lesions in lymph nodes from neck dissections for another malignancy, out of which 3 turned out to be papillary carcinoma.

Contrary to many authors, Leon *et al*[20] found an occult papillary carcinoma in only one out of 11 cases of thyroid inclusions in cervical nodes. However, morphologically, 5 out of 11 cases were compatible with metastases of an occult PTC while 6 cases were benign thyroid inclusions. The incidence of unsuspected thyroid tissue in lymph nodes of patients with head and neck cancers was found to be 1.5%. They suggested that incidental detection of thyroid tissue in such patients does not necessarily indicate need for aggressive therapy.

Occasionally, in cervical lymph nodes, squamous epithelial inclusions may be found. These may be seen either as nests of cells or cysts lined by keratinizing stratified squamous epithelium (Fig. 1).[21,22] Mesothelial cell inclusions may very rarely be found in cervical lymph node.[23]

Axillary Lymph Nodes

Breast tissue inclusions are the most frequently encountered inclusions in the axillary lymph nodes.[9,24-27] Other types of inclusions include occasional reports with squamous inclusion cysts in axillary nodes.

Breast tissue inclusions are composed of ectopic mammary glands and ducts with variable morphological features. Usually, the ducts are lined by dual layers of cells comprising of luminal epithelial cells and basal myoepithelial cells.

Fellagara *et al*[9] reported 18 cases of benign epithelial inclusions in axillary lymph nodes. Thirteen of these patients had coexistent or antecedent breast lesions and therefore underwent nodal sampling. Rest of the patients had enlarged axillary masses without any evidence of breast disease. They classified the nodal inclusions into 3 main categories: glandular type inclusions, squamous cyst and mixed glandular squamous type inclusions.

Ectopic breast tissue may be a cause of false positive axillary sentinel lymph nodes. These maybe misinterpreted as micrometastasis from breast carcinoma. Maiorano e*t al*[27] reported seven cases of ectopic breast tissue in axillary sentinel lymph nodes. In three cases, coexistent micrometastases were detected while in the remaining four cases they were considered benign inclusions. They concluded that a false positive identification of these inclusions as metastatic carcinoma can be prevented by using immunohistochemical markers for myoepithelial component.

Carter *et al*[28] proposed that the presence of tiny clusters of epithelial cells in subcapsular sinus of lymph nodes could be due to many possible reasons: (1) it may represent metastasis with implications of distant metastasis, (2) may represent regional metastasis with less obvious implications for distant disease, (3) may represent epithelial inclusions of embryologic histogenesis or (4) lastly, as proposed by the authors, due to a forced habitation as a result of tumor disruption and displacement into nearby lymphatic vessels. The authors believed that this phenomenon, in itself, does not carry risk of future metastatic behavior.

The occurrence of benign squamous epithelial inclusions in axillary lymph nodes have been

reported by several authors.[29-32] In such cases, cysts have been found lined by keratinizing stratified squamous epithelium without any evidence of nuclear atypia. There has been an occasional report of mullerian inclusions in axillary lymph nodes.[33] Nevus cell aggregates have also been rarely encountered in axillary lymph nodes.[34,35]

Mediastinal Lymph nodes

Benign mesothelial cells in mediastinal lymph nodes were first described by Brooks *et al*[7] in 1990. Mesothelial cell inclusions are most commonly detected in the mediastinal lymph nodes[36-40], but other LN that maybe involved include internal mammary, renal hilar nodes, periaortic and pelvic lymph nodes. Some of these cases are associated with pleural effusions and lymph node inclusions were thought to be pleural cells which have entered lymphatics and reached lymph nodes. The mesothelial origin of these inclusions sometimes needs confirmation by immunohistochemistry and ultrastructural studies. Mesothelial cells show positive staining for calretinin, HBME-1 and cytokeratin 5/6.[41,42]

A serious diagnostic problem for the pathologists is to distinguish these inclusions from metastatic carcinoma and malignant melanoma. Misdiagnosis should be avoided by the awareness of this entity as it can lead to unnecessary side effects of overenthusiastic treatment for the malignant condition.

Peritoneal and Pelvic lymph nodes

Benign inclusions of glandular origin have been observed in the peritoneal and pelvic nodes.[1,5,10,43,44] The epithelial cells are arranged in solid nests or acini and ducts lined by cuboidal to columnar cells. This can result in misinterpretation of metastatic adenocarcinoma at times. Usually the inclusions are few involving a single node and are found in and near the capsule with a typical bland appearance. However, on rare occasions, they may be numerous in the lymphoid parenchyma and thereby mimicking a metastatic carcinoma.

According to Chen *et al*[44], glandular metaplasia from totipotential subcoelomic mesenchyme is the most likely mechanism as there was absence of mesothelial surface involvement and lack of mesothelial inclusions in periaortic lymph nodes. Kheir *et al*[10] studied paraaortic and pelvic lymph nodes removed surgically from 50 female patients for glandular inclusions. They observed inclusions in seven patients, most of which were located in the cortical or capsular regions and were few in number. Only one of their patients developed exuberant inclusions which were initially interpreted as metastatic adenocarcinoma and salpingitis isthmica nodosa. They suggested a definite relationship between tubal disease and glandular inclusions in lymph node. Two mechanisms were proposed to explain this phenomenon: benign metastasis of tubal epithelium to the draining LN and secondly, a proliferative stimulus responsible for salpingitis isthmica nodosa also acting on preexisting glandular inclusions to produce extensive lesions.

Maasen *et al*[5] screened pelvic and paraaotic nodes of 499 gynecological cancer patients for the occurrence of metaplastic changes. They observed glandular inclusions uniformally in all lymphatic areas without any correlation to extent of cancer or any specific type of cancer. In most of their cases, inclusions appeared benign and posed no difficulty in differentiation from metastasis.

In addition to glandular inclusions, pelvic lymph nodes sometimes show decidual tissue inclusions. Burnett *et al*[45] described decidual changes in pelvic lymph node from a pregnant patient with cervical carcinoma.

Benign mesothelial inclusions have been reported in pelvic lymph nodes on several occasions.[46-49] They have been reported in patients with ovarian borderline tumors (both serous[48] and mucinous[49]), struma ovarii[47] and sertoli leydig cell tumors.[46] A feature common to most of the reported cases was a chronic mesothelial irritation caused by either an inflammatory or a neoplastic process. Mesothelial cells usually gain access to the lymph nodes through expansion of lymphatic channels.[7,41]

Benign mullerian inclusions have also been reported in pelvic and paraaortic lymph nodes. Reich *et al*[6] studied a total of 114 patients who underwent surgery for gynecologic cancers. 23% of these patients had benign mullerian inclusions, most commonly in paraaortic nodes followed by external iliac and common iliac regions. These inclusions were commonly observed in patients with ovarian and cervical carcinomas.

Moore *et al*[50] reported 62 cases of mullerian inclusion cysts (MIC) in patients with gynecologic malignancies. MIC are small cysts lined by a serous (mullerian) type, cuboidal to columnar cells with bland nuclear morphology. Out of the 62 cases, 27 were found in lymph nodes. In 70% of these patients, the primary tumor was in the ovary and most frequently of borderline type. The lymph nodes most often involved by MIC were from para

aortic site, which is the primary drainage area for the ovary. In addition, 40% of these paraaortic nodes with inclusions showed associated separate foci of metastasis. Therefore, the authors concluded that MIC, in some cases, instead of being benign more likely represent bland appearing forms of metastatic tumor.

Renal lymph nodes

Epithelial inclusions and Tamm Horsfall proteins deposits are sometimes found in lymph nodes in renal region.[51-54] Zanetti[51] observed an unusual histological pattern in several lymph nodes removed with renal tumours comprising of tubular structures and clusters of apparently epithelial cells floating within sinusoidal deposits of Tamm-Horsfall (TH) protein. They suggested that these inclusions originated from renal tubular epithelium and are transported to paranephric lymph nodes along with TH protein. Yokoushina *et al*[52] reported a series of 3 cases with benign renal tubular epithelial inclusions in nodal sinuses of perinephric lymph nodes of pediatric patients with Wilms' tumors.

Weeks *et al*[53] observed benign mesothelial or coelomic inclusions similar to those described in pelvic and periaortic lymph nodes in nodes of four pediatric patients. It is important to recognize these pseudometastatic lesions to avoid unnecessary and potentially hazardous therapy.

Peripancreatic lymph nodes

Epithelial inclusions in peripancreatic lymph nodes are quite uncommon. Only a limited number of cases have been reported in the literature.[55-57] These cases have been reported in association with a variety of lesions like serous cystadenoma pancreas, adenocarcinoma pancreas, peptic ulcers, common bile duct carcinoma etc. The epithelial inclusions can be either small nests of stratified squamous epithelial cells or glandular formations lined by cuboidal to columnar cells.

Inguinal nodes

Glandular epithelial inclusions have been documented in inguinal lymph nodes by several authors.[58,59] These inclusions comprise of tubular formations in lymph nodes, lined by a single layer of cuboidal to columnar epithelium. Occasionally, malignancies have been reported to arise in the setting of benign inclusions. Casey *et al*[59] reported a case of papillary serous cystadenocarcinoma arising in benign glandular inclusion cysts in pelvic and inguinal lymph nodes in a 65 year old female.

The occurrence of nevus cell aggregates in lymph nodes has been known to occur since 1931. Nevus cells have been found most often in axillary lymph nodes, but they also have been identified in cervical and inguinal regions.[35,60] Nevus cells have been observed in lymph nodes from patients with no known malignancy, as well as in regional lymph nodes draining the carcinoma of the tonsil, tongue[61] etc. The nevus cell aggregates are most commonly located in the capsule or trabeculae of lymph nodes. Usually hematoxylin and eosin stain is sufficient to diagnose nevus cell aggregates, but in some cases they are identified using immunohistochemistry. The nevus cells show positivity for S-100 or MART-1. To differentiate them from metastatic melanoma cells, proliferation marker Ki-67 may be used which tends to be negative in nevus cell inclusions. Two theories have been proposed to account for the presence of nevus cells arrive in or around lymph nodes (1) arrested migration of neural crest progenitor cells during embryonic development and (2) transport of cells from cutaneous lesions to lymph nodes, also termed mechanical transport or benign metastasis.

CONCLUSION

The presence of epithelial inclusions in lymph nodes of various locations sometimes causes significant difficulties in differentiation from metastasis of a malignancy, especially on frozen sections. However, the diagnostic features of benign inclusions like bland nuclear cytology, absence of mitosis, necrosis and desmoplastic stromal reaction help in arriving at a correct diagnosis. The accurate diagnosis of these benign epithelial inclusions is of utmost clinical importance as the misinterpretation of such lesions can result in inappropriate treatment. Hence, it is very important to create awareness of this rare entity among pathologists to prevent misdiagnosis or over diagnosis of a malignant lesion.

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