Lymph node fine needle cytology in the diagnosis of infectious diseases and reactive unspecific processes

Ciro Cipullo1, Bruno Amato2, Elena Vigliar1, Vincenzo Di Crescenzo3, Pio Zeppa1

1Dipartimento di Scienze Biomorfofiche e Funzionali,
Facoltà di Medicina e Chirurgia;
2Dipartimento di Chirurgia Generale, Geriatrica, Oncologica e Tecnologie avanzate,
Università degli Studi di Napoli “Federico II”, Napoli;
3Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno, Salerno, Italia

BACKGROUND

Lymphadenopaties may arise along infectious diseases as expression of hyperplasia and hypertrophy of the immune system. These are usually benign and reversible processes caused by a wide variety of bacteria, mycobacteria, viruses, and parasites. Clinical evaluation and serological data, combined with non-invasive imaging procedures such as ultrasound (US), as well as with Power Doppler or computed tomography (CT), are generally sufficient to the diagnostic assessment of reactive lymph nodes. Nonetheless, in some cases, clinical presentation and imaging are not sufficient to explain the origin and the nature, mainly in case of persistent lymph node enlargement and atypical clinical presentation; suspected lymphoproliferative processes or doubts about the lymph nodal nature of the nodule may require further investigation. The number and sites of the lymph node involved by an infectious disease are extremely variable, as well as the entity and the duration of the enlargement. In fact, during or after a recent infection, children may develop significant and persistent lymph node enlargement. Conversely, adults generally develop less evident reactive enlargements; hence any persistent lymph node enlargement in adults, in an undefined clinical context, should be considered suspicious for different etiologies including lymphoproliferative processes. Surgical excision and histological control represent the gold standard in the diagnosis of lymphadenopaties, but they might be unnecessary procedures for pure diagnostic purposes in the benign reactive lymph nodal enlargement [1]. Fine Needle Cytology (FNC) is a steady procedure in the diagnostic algorithm of diseases of most organs and tissues and, combined with different ancillary techniques, has gained a definitive role in the diagnosis of lymphadenopaties [2-25].

FINE NEEDLE CYTOLOGICAL FINDINGS

Cytological features in benign reactive lymphadenopaties are often unspecific, showing a variable mixture of normal lymph node cell type constituents, vascular structures and phagocytising histiocytes which confer a polymorphous appearance of the smear. These aspects are not indicative of any specific etiology but may be sufficient in some cases to exclude any malignancy. In monomorphous patterns, cytopathology alone is not sufficient to exclude a lymphoproliferative process (Figure 1), mainly a low grade non Hodgkin lymphoma. In these cases ancillary techniques (Figure 2) and/or lymph node excision have to be performed for a definitive diagnosis. Granulomatous and supplicative cytological patterns can exclude neoplastic processes and may also be indicative of specific etiologic agents [26-28]. An example of a quite
specific lymph node cytological pattern is the one observed in infectious mononucleosis which can cause cervical or generalized lymphoadenopathy and splenomegaly. Smears usually show a great amount of immunoblasts with large nucleoli and a rim of blue cytoplasm, as well as a background of normal cell type constituents, including centrocytes and centroblasts. Macrophages and capillary structures may be present. Other features include mitotic figures and occasional binucleated forms. These latter may be numerous and atypical in their cytological resembling those observed in Hodgkin lymphoma (HL); therefore, a differential diagnosis may be pointed out. However, HL has a cytological polymorphous background of mature lymphocytes and follicular centre cells, a variable amount of neutrophils and eosinophils and lacks extensive immunoblastic proliferation which is more consistent with infectious mononucleosis [26]. Other viral infections and post-vaccinal conditions can result in lymph node enlargement, but they seldom offer specific patterns: in these cases, FNC shows small mature lymphocytes intermingled with centrocytes and centroblasts, plasmacells and immunoblasts. Capillary structures, phagocytizing histiocytes and eosinophils may be present. Bacterial infections generally produce regional suppurative lymphadenopathies. FNC shows neutrophil granulocytes and a variable amount of lymphocytes in a necrotic background. Differential diagnosis should include metastatic squamous cell carcinoma and rarely HL, which can show a prevalent necrotic-suppurative background. Granulomatous lymphadenitis may be determined by several infective agents, tuberculosis being the most frequent. Differential diagnostic problems about granulomatous lymphadenitis may arise because of the presence of morphologic components such as epithelioid cells, multinucleated giant cells, and necrotic material shared between different infectious diseases and not (i.e. sarcoidosis). Different entities can be distinguished on the basis of subtle cytomorphic features and with the aid of ancillary techniques. Smears from lymph nodes involved by tuberculosis show epithelioid cells and/or multinucleated giant cells, either isolated or in a granulomatous arrangement in a lymphoid background. Diagnosis can be suspected by cytomorphic features of well-formed epithelioid granulomas and by the presence of caseous necrosis. These findings help in diagnosis of tuberculosis but the demonstration of acid-fat bacilli by Ziehl-Neelsen or mycobacterial culture or PCR remain mandatory in establishing the diagnosis. Another condition in which FNC is a valid diagnostic support is cat-scratch lymphadenitis. The cytological features of cat-scratch disease include typical granulomas, with peripherally palisading epithelioid histiocytes and centrally located neutrophils, and an associated polymorphic lymphoid cell population. Lymphadenitis due to Toxoplasma...
Infection should be considered in the diagnosis of lymphadenopathy, especially in the cervical region. FNC shows as distinctive features numerous epithelioid cells, either isolated or in small clusters (microgranulomas). Occasional histiocytes containing organism resembling trophozoites may be observed; usually, necrosis does not occur.

**CONCLUSIONS**

FNC is a minimally invasive, cost-effective, helpful procedure in the differential diagnosis of reactive lymphadenopaties including those caused by infectious agents. Nonetheless, it requires a complete knowledge of the clinical context, the availability of ancillary techniques and experienced cytopathologists aware of the possibilities and limitations of the procedure. Lymph node FNC may be helpful in the diagnosis of lymph nodal reactive hyperplasia with infective aetiology, thus preventing, when possible, unnecessary excisional biopsy.

**Keywords:** lymph node, fine needle cytology, infectious diseases.

Conflict of interest disclosure: The authors declare that the article has not been sponsored, that no financial support has been given and finally that there is no conflict of interest.

**SUMMARY**

Infectious diseases are one of the main causes of lymph node enlargement both in children and adults and represent a benign and reversible process. Clinical evaluation, serological data, microbiological and molecular tests and imaging techniques are generally used in the diagnosis of reactive lymph nodes determined by infectious diseases but, in some cases, do not assess their origin and nature. Surgical excision and histological control represent the gold standard in the diagnosis of lymphadenopaties, but they might be unnecessary procedures just for diagnostic purposes in benign reactive lymph nodal enlargement. Fine Needle Cytology (FNC) has gained a definitive role in the diagnosis of lymphadenopaties being an accurate, rapid, minimal invasive and cost-effective procedure useful for the clinical management and therapeutic decisions. This study reports the use of FNC in the diagnosis of reactive lymph nodes in infectious diseases, exploring possibilities and limitations of the technique in this specific clinical setting.

**REFERENCES**


