

Lymph node fine needle cytology in the diagnosis of infectious diseases: clinical settings

Citologia per ago sottile dei linfonodi nella diagnosi delle malattie infettive: aspetti clinici

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■ BACKGROUND

Fine needle cytology (FNC) is widely used in the diagnosis of different organs and pathologies [1-18]. Lymph nodes are also being more and more used to diagnose benign reactive conditions in non-surgical diseases, such as infections or other benign conditions. Coupled with an accurate clinical history, physical examination and ancillary techniques, when needed, FNC of enlarged nodes provides sufficient information to allow keeping the lymph node, clinical surveillance and medical treatment, when needed.

Lymphadenopathies, in both adults and children, are a common problem in the clinical practice and may be due to different causes. The most common cause is represented by a non-specific reactive hyperplasia probably due to an asymptomatic inflammatory process or by specific infectious agents that disappear before they can be clinically or radiologically detected. Infectious agents include pyogenic bacteria, mycobacteria, fungi, cat-scratch disease, toxoplasmosis, HIV and infectious mononucleosis [19-23].

Technical aspects

FNC lymph node of palpable lymph nodes should be performed by the cytopathologist after the clinical evaluation and after a detailed anamnesis of the patient, as reported in another article of the issue. In case of impalpable and/or deep located lymph node, FNC will be

performed under ultrasound (US) or computed tomography (CT) control; in both cases, rapid on-site evaluation (ROSE) of the smears should be performed. ROSE ensures the adequacy of the sample for cellularity and an initial diagnostic orientation in order to perform additional passes, when needed, and to address specific ancillary techniques. For example, if an infection is suspected additional material may be obtained for culture.

Cytological features

Smears are generally air dried and alcohol fixed for specific stains; air dried smear are immediately stained by Diff-Quik. This latter stain is a Romanowsky modified stain that is performed in a couple of minutes.

ROSE of these smears is able to confirm the adequacy of the smear and an initial diagnostic orientation.

At low magnification cellularity, cell patterns and background material (e.g. necrosis, inflammatory debris) are generally evaluated. In case of reactive hyperplasia, the presence of epithelioid cells or lympho-histiocytic aggregates containing dendritic cells are helpful in the diagnosis of reactive hyperplasia.

At high magnification, nuclear and cytoplasmic features are evaluated; this allows to identify specific cell subtypes such as follicular centre cells, reticular cells, granulocytes, small lymphocytes and macrophages, as well as their size, shape, chromatin pattern and nucleoli. Benign processes caused by infectious agents tend

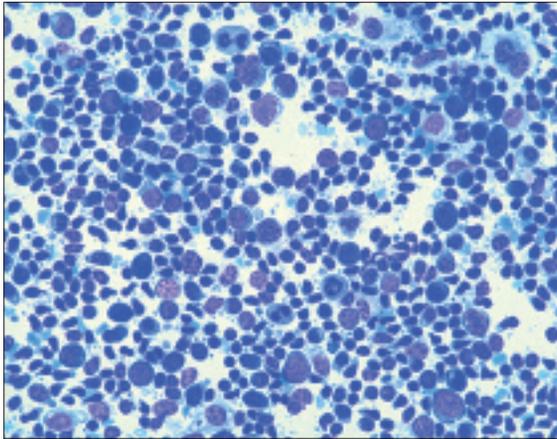


Figure 1 - Cytological features of reactive follicular hyperplasia. Numerous follicular centre cells are present intermingled with mature lymphocytes. These cases are indistinguishable from lymphomas on the sole cytological presentations and need ancillary techniques to be correctly diagnosed (Diff Quik stain 430X).

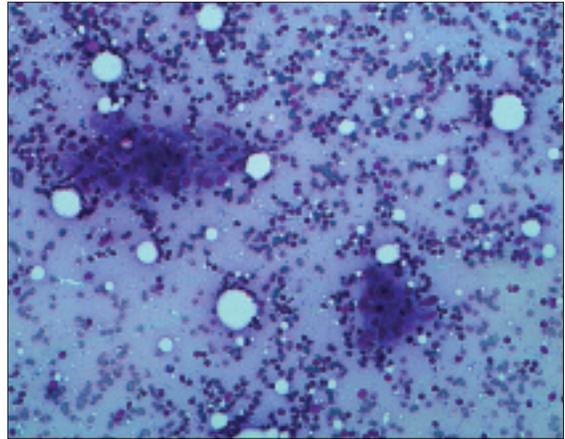


Figure 2 - Cytological features of a reactive granulomatous lymph node; note small groups of epithelioid cells and mature lymphocytes in the background (Diff-Quik stain 270X).

to be more polymorphous, showing a predominance of small lymphoid cells, and a variable amount of macrophages.

A quite polymorphous smear, in a proper clinical and imaging setting may be sufficient to diagnose a reactive hyperplasia in much of the cases. When the smear is relatively monomorphous, with large centrollicular cells (Figure 1) and/or does not match with clinical data and imaging, immunophenotyping of the cells by flow cytometry (FC) is performed to assess cell polyclonality. The presence of a heterogeneous population of lymphoid cells allows morphologically to hypothesize the etiology of a benign lymphadenopathy evaluating the presence of an increased proportion of plasma cells, macrophages or eosinophils in a clean or necrotic and granulomatous or non-granulomatous background.

Lymphadenitis are clinically classified as acute and chronic, and cytological presentations often reflects the clinical one. Acute lymphadenitis generally shows polymorphous smears with prevalence of one of the above reported cell types; when the lymphadenitis is maintained by pyogenic bacteria a variable amount of granulocytes is detected. Granulocytes generally infiltrate the sinuses and the lymph node stroma, and are associated to follicular hyperplasia. In corresponding smears, a variable amount may be detected ranging between a definite amount intermingled between all other cells and a complete prevalence, conferring a suppurative as-

pect to smears. Chronic lymphadenitis are generally classified into non-granulomatous (Figure 2) and granulomatous; in this latter, the structure of the lymph node may be partially or completely subverted by confluent granulomas with or without necrosis.

Corresponding smears will reflect these aspects showing necrotizing (necrotic/dirty background) or non-necrotizing (clean background) smears.

When a granulomatous pattern is observed, attention should be paid to the detection of eosinophils and atypical mono or binucleated cells that may reveal an unsuspected Hodgkin lymphoma.

Necrotic background may be purulent as in tularemia, lymphogranulomatosis venereal groin (LVG), cat-disease, Kikuchi disease and lymphadenitis of Maschoff-Knopp; it can be caseous in cases of typical and atypical mycobacteria infections.

Among the non-necrotizing granulomatous lymphadenitis, the most common are tuberculoid leprosy, fungal infection and atypical mycobacteria.

Chronic non-granulomatous lymphadenopathy can be systematized according to clean or necrotic/dirty background. A heterogeneous lymphoid population with clean background may be a viral infection, such as mononucleosis, lymphadenitis post-vaccination, and syphilis; instead, if a heterogeneous lymphoid population is accompanied by eosinophils,

with presence of eosinophilia, this may be a parasite infection. When there are numerous histiocytes in a polymorphic framework, whipple disease, atypical mycobacteria, lepromatous-histiocitoid leprosy, histoplasma, and atypical mycobacteria are taken into consideration.

Moreover, in the case of lymphadenitis with a heterogeneous lymphoid population and a necrotic background (necrotizing lymphadenitis) with neutrophils, early cat scratch disease, tuberculosis, atypical mycobacteria, filaria, and HSV are taken into consideration. Instead, Kikuchi lymphadenitis and pneumocystis infection are characterized by a polymorphous population without neutrophils [19, 22]. These cytological presentations may suggest a possible etiology but are specific and diagnostic of a specific agent. Additional passes and residual material may be used for microbiological or molecular testing for specific antigens.

CONCLUSIONS

FNC of lymph nodes is a simple and useful tool in the assessment of enlarged lymph node, providing that an expert cytopathologist performs the FNC, evaluates the smears by ROSE and requires ancillary techniques, when needed, on the basis of the specific clinical context and cytopathological features. When these conditions are met, reactive lymph nodes FNC may be useful because, excluding possible lymphomas or metastases, it allows to avoid useless biopsies and appropriate therapies.

Keywords: lymph node, fine needle cytology, infectious diseases, clinical setting.

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SUMMARY

Lymph node reactive hyperplasia, caused by specific infectious etiologic factors, represents the most frequent cause of enlarged peripheral lymph nodes. The main infectious agents are viruses, pyogenic bacteria, mycobacteria, fungi and protozoa that may determine unspecific or specific pathological entities, such as cat-scratch disease, toxoplasmosis or infectious mononucleosis. Lymph node fine needle cytology (FNC) is a safe, simple, cost-effective and efficient technique that quickly

provides information about the cell population and the nature of the process. FNC can also provide suitable material for ancillary techniques, such as flow cytometry, immunocytochemistry, molecular biology and microbiological examinations.

This study focuses on the cytological features of benign lymphadenopathy of infectious origin and their possible contribution to the clinical setting definition of corresponding patients.

RIASSUNTO

Le iperplasie reattive linfonodali causate da diversi agenti microbiologici rappresentano la prima causa di ingrandimento linfonodale. Gli agenti infettivi responsabili sono rappresentati da virus, batteri piogeni, micobatteri, funghi e protozoi che possono determinare entità patologiche specifiche quali la malattia da graffio di gatto, la toxoplasmosi, la mononucleosi o entità non specifiche. La citologia per ago sottile (FNC) è una metodica semplice, economica ed efficace che può fornire informazioni rapide sui costituenti cellulari del linfonodo e sulla natura della corrispondente iperplasia. FNC può an-

che essere utilizzata per acquisire materiale utile per tecniche ancillari applicate quali citometria a flusso, immunocitochimica e tecniche microbiologiche e molecolari. Queste metodiche sono spesso indispensabili per diagnosticare la natura del processo stesso e possibilmente gli eventuali agenti biologici. Questo studio è focalizzato sugli aspetti citologici delle linfadenopatie benigne, reattive, sulle possibili relazioni con i corrispondenti agenti microbiologici e sul contributo che la metodica può fornire alla definizione del contesto clinico e delle strategie terapeutiche.

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