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Lymph node fine needle cytology in the diagnosis of infectious diseases: cytological and histological correlations

Citologia per ago sottile dei linfonodi nella diagnosi delle malattie infettive: correlazioni cito-istologiche

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BACKGROUND

Fine needle cytology (FNC) is an minimally invasive procedure used in the diagnosis of different organs and pathologies [1-18]. When applied to lymph nodes enlargement, FNC may diagnose reactive hyperplasia, granulomatous lymphadenopathies, primary lymphoid malignancies and metastatic diseases. In case of reactive hyperplasia, surgical excision is generally not indicated, unless the course is atypical or in case of significant discrepancies between clinical data, imaging and FNC findings.
A specific diagnosis can be made in many cases of infectious processes by FNC, which provides material for further cytomorphologic analysis and ancillary studies [19-25].
Cytological features may be indicative or not of corresponding histological features depending on the specific aetiology and the different lymph nodal compartment mainly involved in the process.

CYTOLOGICAL AND HISTOLOGICAL FINDINGS

The most common histological pattern of reactive lymph node is the follicular hyperplasia, in which there is a prevalence of polymorphous and well-delineated follicles. These follicles show large germinal centres circumscribed by an evident layer of small lymphocytes. Corresponding cytological smears show a heterogeneous and polymorphous cell population represented by immature medium size lymphocytes centroblasts and immunoblasts. Cytological corresponding smears show a proportional prevalence of these cells with some cytological differences due to the different kind of samples.
When the polymorphous pattern is not evident (Figure 1) the differential diagnosis with a low grade, follicular lymphoma or other low-grade non-Hodgkin lymphomas is pointed out and a definitive cytological diagnosis on the basis of the sole cytological features would be impossible. In these cases ancillary techniques such as flow cytometry (FC) (Figure 2) or polymerase chain reaction (PCR) are needed to assess the polyclonality of the process through the demonstration of light chain proportional expression or policlonality of the heavy chain gene IGH, these procedures can be performed on FNC cell suspensions or additional smears [19-25].
Cytological counterparts of this pattern are not specific enough to be recognized on FNC smears, being represented by a heterogeneous population of small lymphocytes, plasma cells and large lymphoid cells including im-

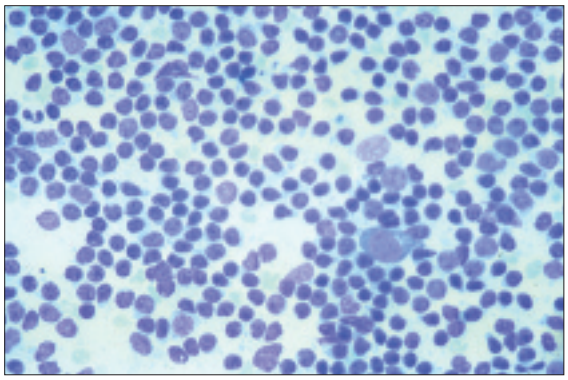

Figure 1 - FNC cytological features of reactive hyperplasia with a relative monomorphous pattern. This case is indistinguishable from lymphoma on the sole cytological presentations and need ancillary techniques to be correctly diagnosed (Diff Quik stain 430X).

munoblasts and intermediate cells in various stages of maturation. The predominant cells are small mature lymphocytes showing a single round nucleus with dense chromatin, inconspicuous nucleoli and a high nucleus/cytoplasm ratio.
Nuclei of the larger lymphoid cells have reticulated chromatin, large nucleoli, and a rim of basophilic cytoplasm.
These cytological presentations are neither specific for the histological counterpart nor for the

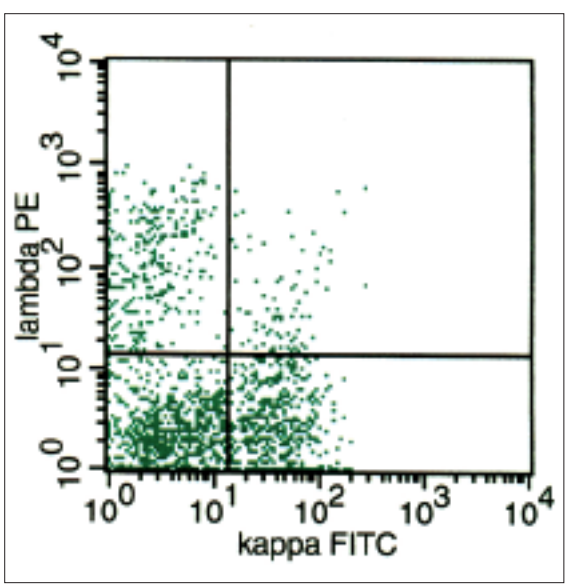

Figure 2 - Flow cytometry assessment of light chain of the case reported in fig. 1 showing balanced kappa and lambda light chains.

possible aetiological agents. Moreover in many cases a differential diagnosis with a lymphoproliferative process is pointed out. In these cases too, selected ancillary techniques are often effective to assess the nature of the process, as reported above.
Indeed, the immunophenotype of florid reactive hyperplasia, performed by FC, will show a variable mixture of B-cells and T-cells expressing a proper antigen repertoire and including balanced light chain expression detectable by FC [19-25].
Notwithstanding these procedures, cases impossible to diagnose may occur and indication for a direct histological examination should be given to avoid any delay to further investigations and appropriate treatments.
Histological aspects of suppurative lymphadenitis are characterized, in the acute phase, by dilated sinuses containing a weakly pinkish proteinaceous fluid with numerous granulocytes, mostly neutrophils, and macrophages, with congestion of the blood vessels. The neutrophils infiltrate the lymph node parenchyma forming micro abscesses. In the later phase, granulocytes are replaced by lymphocytes, plasma cells and macrophages containing ingested cellular debris. FNC of suppurative lymphadenitis are usually highly cellular with a large numbers of neutrophils that may be intact and/or degenerated.
Degenerative changes can also be observed in lymphocytes and macrophages conferring to the smear a necrotic "dirty" background. Bacteria, which represent most frequent agents may be sometimes visualized, mainly on Romanowsky stained smears in the background or in the cytoplasm of macrophages. In these cases, non-Hodgkin lymphoma can be excluded on the basis of the sole cytological features; instead, other pathologies might be considered in the differential diagnosis according to the clinical presentation.
In fact a suppurative background may hide scattered malignant cells such as malignant squamous cells in metastases from squamous cell carcinoma or Reed-Sternberg cell in the rare pseudo-suppurative variant of Hodgkin lymphoma or other neoplasm with extensive necrosis of corresponding lymph node.
The histological aspects of granulomatous lymphadenopaties are variable due to the presence or absence of caseous necrosis or other necrotizing aspects. In mycobacterium tuberculosis, lymphadenitis exsudative forms, caseous

necrosis containing numerous bacilli and coalescent lesions, and proliferative forms characterized by granulomas containing few bacilli, Langhans cells, epithelioid cells and lymphocytes may occur. Fibrosis, hyalinization and occasional calcification may also be present. In some cases, mainly in atypical mycobacterial lymphadenitis, a large number of neutrophils may be present.
Corresponding cytomorphologic features may be scantily or moderately cellular with presence of epithelioid cells and multinucleated large cells. Epithelioid and multinucleated cells may be isolated or organized, in granulomatous structures on FNC smears too.
Neutrophils may also be present and necrotic debris may be prominent in the background. It has to be stressed that epithelioid and multinucleated giant cells may also be present in other bacterial lymphadenitis, hence different etiologies should be considered in the differential diagnosis of granulomatous lymphadenitis. On additional smears, acid-fast bacilli may be detected by Ziehl-Neelsen whereas even little amount of mycobacteria can be detected by polymerase chain reaction (PCR) using residual cytological material.
Granulomatous pattern should be always carefully evaluated on FNC smears because Hodgkin lymphoma too may occasionally show granulomatous features and corresponding diagnostic cells can be missed in a predominant granulomatous pattern [19-24].

CONCLUSIONS

FNC is a helpful technique for the diagnosis of reactive lymph node enlargements, whereas some limitations should be highlighted. Benign reactive hyperplasia and even specific infectious lymphadenopathies may be hardly or not distinguishable from some low grade non-Hodgkin lymphoma on cytological samples.
A proper usage of ancillary techniques, combined to cytological features, can be helpful to achieve a correct diagnosis in most of the cases. Other more specific cytological presentations may hide different pathological process hence a complete clinical history, expert cytopathologists, rapid on-site evaluation and proper ancillary techniques are needed to perform a safe and accurate FNC of reactive lymph nodes.
Notwithstanding these procedures, FNC unsolvable cases may occur.
In these cases indication for a direct histological examination should be promptly given to avoid any delay to further investigations and appropriate treatments.

Keywords: lymph node, fine needle cytology, cytological patterns, histological correlations.

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SUMMARY

Fine Needle Cytology (FNC) is often used in the diagnosis of lymph node enlargement as first diagnostic procedure. In some cases different cytological features may occur, with different histological aspects.
In other cases, FNC samples are neither representative nor sufficient to exclude a possible lymphoproliferative process or a metastasis. In these cases, specific ancillary techniques such as microbiological tests, immunocytochemistry, flow cytometry or molecular biology procedures may be used to assess the benign reactive nature of lymph node enlargement, allow clinical surveillance and avoid surgical biopsies.
Cytology and ancillary techniques may also identify, in selected cases, possible aetiological agents. Notwithstanding these procedures, FNC unsolvable cases may occur; in these cases, indication for a direct histological examination should be promptly given in order to avoid any delay to further investigations and appropriate treatments.
This study reports the most common cytological patterns occurring in reactive lymph nodes as well as ancillary techniques required in different conditions. Lymph nodal FNC should be performed by expert cytopathologists ensuring a safe and correct execution and a rapid evaluation of the smears for the assessment and the application of specific ancillary techniques.

RIASSUNTO

La citologia per ago sottile (FNC) è generalmente utilizzata nelle diagnosi delle linfoadenopatie come primo presidio microinvasivo per la programmazione diagnostica e terapeutica. I diversi aspetti istologici delle linfoadenopatie reattive sono variamente ed in diversa misura riproducibili su strisci ottenuti da FNC. In alcuni casi gli aspetti citologici ottenuti sono rappresentativi dei corrispondenti istologici, in altri non sono sufficienti né ad identificare il corrispettivo quadro istologico né ad escludere un possibile processo linfoproliferativo. In questi casi è necessario utilizzare specifiche tecniche ancillari di immunocitochimica, citometria a flusso e biologia molecolare per formulare diagnosi di benignità e consentire la sorveglianza clinica e trattamenti evitando biopsie chirurgiche. Tali tecniche, in casi selezionati, possono inoltre contribuire all'identificazione di possibili agenti eziologici. Anche quando queste condizioni sono rispettate, casi irrisolvibili all'FNC possono presentarsi. In questi casi è necessario tempestivamente indicare l'escissione del linfonodo per una diagnosi istologica definitiva. In questo studio sono esaminati e discussi i più frequenti pattern citologici di iperplasie reattive e le tecniche ancillari indispensabili nelle diverse condizioni. La FNC linfonodale dovrebbe essere eseguita da un citopatologo esperto che assicuri una corretta esecuzione del prelievo, dello striscio ed una rapida interpretazione del materiale aspirato che consenta di applicare tecniche ancillari mirate agli specifici contesti clinici e citologici.

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