Le Infezioni in Medicina, Suppl. 3, 30-33, 2012

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

Citologia per ago sottile dei linfonodi nella diagnosi delle malattie infettive e processi reattivi aspecifici

Ciro Cipullo[1], Bruno Amato[2], Elena Vigliar[1], Vincenzo Di Crescenzo[3], Pio Zeppa[1]

[1]Dipartimento di Scienze Biomorfologiche e Funzionali, Facoltà di Medicina e Chirurgia;
[2]Dipartimento di Chirurgia Generale, Geriatrica, Oncologica e Tecnologie avanzate, Università degli Studi di Napoli "Federico II", Napoli;
[3]Dipartimento 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 phagocyting 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 lymphproliferative 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 suppurative cytological patterns can exclude neoplastic processes and may also be indicative of specific etiologic agents [26-28]. An example of a quite

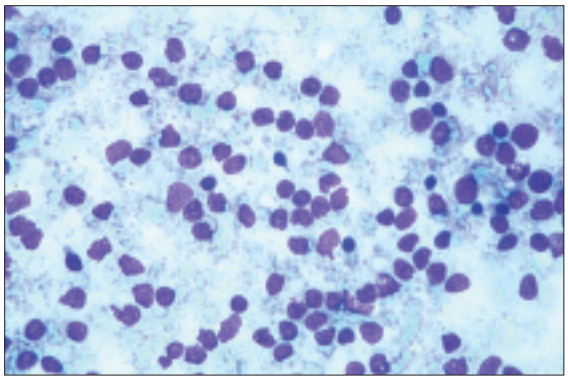

Figure 1 - cytological features of a low-grade non Hodgkin lymphoma: a monomorphous population of small lymphocytes with little or not atypia. This cases would be impossible to distinguish from a reactive hyperplasia and need specific ancillary techniques. (Diff Quik stain 430X).

specific lymph node cytological pattern is the one observed in infectious mononucleosis which can cause cervical or generalized lymphoadenopaty 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

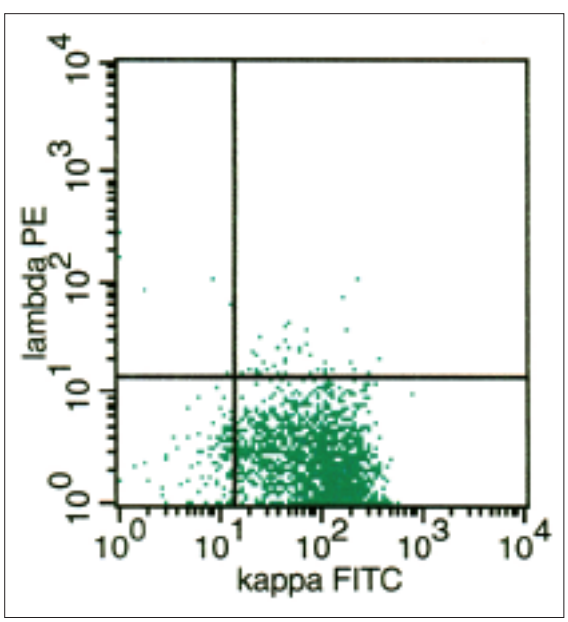

Figure 2 - Flow cytometry assessment of light chain of the case reported in fig. 1 showing restriction for kappa light chain.

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, phagocyting histiocytes and eosinophils may be present. Bacterial infections generally produce regional suppurative lymphadenopaties. 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 cytomorphologic 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 cytomorphologic 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.

RIASSUNTO

Le malattie infettive sono una delle principali cause di linfoadenopatia, sia nei bambini che negli adulti. La valutazione clinica, i dati sierologici, test microbiologici e molecolari e la diagnostica per immagini sono generalmente utilizzati nella diagnosi di linfadenopatie reattive su base infettiva tuttavia non sempre riescono a dirimerne con certezza le cause ed la natura.
La biopsia escissionale e la valutazione istologica rappresentano il gold standard nella diagnosi delle linfoadenopatie, ma possono risultare procedure non necessarie ai soli fini diagnostici in caso di ingrossamenti linfonodali benigni. La citologia per ago sottile (FNC) ha acquisito un ruolo riconosciuto nella diagnosi delle linfoadenopatie in quanto è una metodica accurata, rapida, non invasiva e dai costi limitati estesamente utilizzata in altri campi della patologia umana e nella gestione clinica dei pazienti.
Il presente studio valuta le possibilità e i limiti del FNC nella diagnosi dei processi reattivi linfonodali in corso di malattie infettive.

REFERENCES

[1] Anne S., Teot L.A., Mandell D.L. Fine needle aspiration biopsy: role in diagnosis of pediatric head and neck masses. *Int. J. Pediatr. Otorhinolaryngol.* 72, 1547-1553, 2008.

[2] D'Antonio A., Paolella G., Zeppa P. Rapidly growing intraparotid mass in a young child. *J. Craniofac. Surg.* 4, 305-306, 2012.

[3] Zeppa P., Sosa Fernandez L.V., Cozzolino I., et al. Immunoglobulin heavy-chain fluorescence in situ hybridization-chromogenic in situ hybridization

DNA probe split signal in the clonality assessment of lymphoproliferative processes on cytological samples. *Cancer Cytopathol*. 2012 (in press).
[4] Bellevicine C., Malapelle U., Iaccarino A., et al. Foamy gland pancreatic ductal adenocarcinoma diagnosed on EUS-FNA: A histochemical, immunohistochemical, and molecular report. *Diagn Cytopathol*. 2012 (in press).
[5] Stanzione B., Cozzolino I., Arpino G., Vigliar E., Virginia S.F., Zeppa P. Multiple metachronus proliferative fasciitis occurring in different anatomic regions: a case report and review of the literature. *Pathol. Res. Pract.* 2, 126-130, 2012.
[6] Zeppa P. Haematocytopathology: why? *Cytopathology.* 2, 73-75, 2012.
[7] D'Antonio A., Baldi C., Memoli D., Caleo A., Rosamilio R., Zeppa P. Fine needle aspiration biopsy of intraparotid spindle cell lipoma: A case report. *Diagn. Cytopathol*. 2011.
[8] Zeppa P., Barra E., Napolitano V., et al. Impact of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in lymph nodal and mediastinal lesions: a multicenter experience. *Diagn. Cytopathol*. 10, 723-729, 2011.
[9] Vigliar E., Bellevicine C., Cozzolino I., Zeppa P. Histological and fine needle aspiration cytological features of Hashimoto thyroditis-associated 'angiomatoid' papillary thyroid carcinoma. *Cytopathology*. 2012 (in press).
[10] Zeppa P., Vigliar E., Cozzolino I., et al. Fine needle aspiration cytology and flow cytometry immunophenotyping of non-Hodgkin lymphoma: can we do better? *Cytopathology.* 5, 300-310, 2010.
[11] Zeppa P., Cozzolino I., Peluso A.L., et al. Cytologic, flow cytometry, and molecular assessment of lymphoid infiltrate in fine-needle cytology samples of Hashimoto thyroiditis. *Cancer* 3, 174-184, 2009.
[12] Troncone G., Guerriero E., Pallante P., et al. UbcH10 expression in human lymphomas. *Histopathology.* 54, 731-740. 2009.
[13] Malapelle U., Bellevicine C., Zeppa P., Palombini L., Troncone G. Cytology-based gene mutation tests to predict response to anti-epidermal growth factor receptor therapy: a review. *Diagn. Cytopathol.* 9, 703-710, 2011.
[14] Vigliar E., Cozzolino I., Fernandez L.V., et al. Fine-needle cytology and flow cytometry assessment of reactive and lymphoproliferative processes of the breast. *Acta Cytol.* 2, 130-138, 2012.
[15] Schmitt F., Vielh P., Zeppa P. Cytology for pathologists: two sides of the same coin or different views of the same side? *Cytopathology.* 5, 345-346. 2012.
[16] Cozzolino I., Zeppa R., Zeppa P. Lymph nodal Merkel cell carcinoma: primary tumor or metastasis from unknown primary site? *J. Cutan. Pathol.* 10, 836-837, 2011.
[17] Cozzolino I., Nappa S., Picardi M. et al. Clonal B-cell population in a reactive lymph node in acquired immunodeficiency syndrome. *Diagn. Cytopathol.* 12, 910-914, 2009.
[18] Petruzziello F, Zeppa P, Ciancia G et al. Cytological and histological detection of amyloid deposits in bone marrow of patients affected by multiple myeloma. *Leuk. Lymphoma.* 52: 2304-2307. 2011.
[19] Zeppa P., Varone V., Cozzolino I. et al. Fine needle cytology and flow cytometry of ectopic cervical thymoma: a case report. *Acta Cytol.* 54, 998-1002, 2010.
[20] Rimm D.L., Stastny J.F., Rimm E.B., Ayer S., Frable W.J. Comparison of the costs of fine-needle aspiration and open surgical biopsy as methods for obtaining a pathologic diagnosis. *Cancer* 81, 51-56, 1997.
[21] Saboorian M.H., Ashfaq R. The use of fine needle aspiration biopsy in the evaluation of lymphadenopathy. *Semin. Diagn. Pathol.* 18, 110-123, 2001.
[22] Gupta R.K., Naran S., Lallu S., Fauck R. Diagnostic value of needle aspiration cytology in the assessment of palpable axillary lymph nodes. A study of 336 cases. *Acta Cytol.* 47, 550-554, 2003.
[23] Schafernak K.T., Kluskens L.F., Ariga R., Reddy V.B., Gattuso P. Fine-needle aspiration of superficial and deeply seated lymph nodes on patients with and without a history of malignancy: review of 439 cases. *Diagn. Cytopathol*. 29, 315-9, 2003.
[24] Thomas J.O., Adeyi D., Amanguno H. Fine-needle aspiration in the management of peripheral lymphadenopathy in a developing country. *Diagn. Cytopathol.* 21, 159-162, 1999.
[25] Steel B.L., Schwartz M.R., Ramzy I. Fine needle aspiration biopsy in the diagnosis of lymphadenopathy in 1,103 patients. Role, limitations and analysis of diagnostic pitfalls. *Acta Cytol.* 39, 76-81, 1995.
[26] Stanley M.W., Steeper T.A., Horwitz C.A., Burton L.G., Strickler J.G., Borken S. Fine-needle aspiration of lymph nodes in patients with acute infectious mononucleosis. *Diagn. Cytopathol*. 6, 323-329, 1990.
[27] Viguer J.M., Jiménez-Heffernan J.A., López-Ferrer P., González-Peramato P., Vicandi B. Fine needle aspiration of toxoplasmic (Piringer-Kuchinka) lymphadenitis: a cytohistologic correlation study. *Acta Cytol*. 49, 139-143, 2005.
[28] Mittal P., Handa U., Mohan H., Gupta V. Comparative evaluation of fine needle aspiration cytology, culture, and PCR in diagnosis of tuberculous lymphadenitis. *Diagn. Cytopathol*. 39, 822-826, 2011.