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Fine needle aspiration (FNA) cytology in tuberculous lymphadenitis

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Sixty-three lymph node aspirates were screened and 32 aspirates revealing granulomatous lymphadenitis with or without caseation necrosis were re-evaluated. The most characteristic morphological features among these cases were epithelioid cell clusters with or without caseation necrosis. When clusters were thick, careful observation of the periphery of the clusters helped to find epithelioid cells. Caseation necrosis revealed a typical macroscopic and microscopic appearance. Ziehl–Neelsen staining was negative in all smears and histological sections. Polymerase chain reaction (PCR) amplification technique was applied to 23 of the cases in which the cytological diagnoses were consistent with tuberculosis. *Mycobacterium tuberculosis* was demonstrated in 19 (82.60%) cases. In conclusion: (i) it is necessary to perform several aspirations from different sites of the enlarged lymph node; (ii) the diagnosis of 'granulomatous lymphadenitis, consistent with tuberculosis' can be given, even though the acid-fast stains are negative; (iii) additional techniques such as PCR give supportive information; (iv) an open biopsy is recommended if there is a discrepancy with the clinical impression.

Keywords: fine needle aspiration, granulomatous lymphadenitis, tuberculosis

Cytologie par ponction à l'aiguille fine de la lymphadénite tuberculeuse

Dans ce travail, 63 ponctions ganglionnaires dont 32 présentaient un tableau de lymphadénite granulomateuse avec ou sans nécrose caséeuse ont été réexaminées. Parmi ces cas, les critères morphologiques les plus caractéristiques sont la présence de groupes de cellules épithélioïdes avec ou sans nécrose caséeuse. Lorsque les agrégats sont épais, l'observation attentive de la périphérie des amas permet de trouver les cellules épithélioïdes. La nécrose caséeuse présente un aspect macroscopique et microscopique caractéristique. La coloration acid-fast s'est révélée négative dans tous les frottis et dans les coupes histologiques. La technique d'amplification par PCR a été appliquée à 23 de ces cas, pour lesquels le diagnostic cytologique était compatible avec une tuberculose. La présence de Mycobactérium tuberculosis a été démontrée dans 19 cas (82,6%). En conclusion: 1- il

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est nécessaire de réaliser des cytoponctions dans plusieurs directions au niveau du ganglion pathologique; 2- le diagnostic de "lymphadénite granulomateuse compatible avec une tuberculose" peut être proposé même si la coloration acid-fast est négative; 3- des techniques complémentaires telles que la PCR peuvent donner une information supplémentair; 4- la biopsie chirurgicale sera recommandée s'il existe une discordance avec les données cliniques.

Mots clés: Ponction a l'aiguille fine, lymphadénite granulomateuse, tuberculose

Feinnadelpunktate bei tuberkulöser Lymphadenitis

63 LK-Aspirate wurden ausgewertet und 32 mit Zeichen einer granulomatösen Lymphadenitis überprüft. Morphologische Kennzeichen waren Epitheloidzellgruppen mit oder ohne verkäsende Nekrose. Bei dichteren Verbänden lassen sich die Epitheloidzellen in der Peripherie nachweisen. Die käsigen Nekrosen bieten ein typisches makroskopisches und mikroskopisches Bild. Säurefeste Stäbchen waren weder in den Ausstrichen, noch in den Schnitten nachweisbar. Die PCR-Technik wurde in 23 zytologisch positiven Fällen eingesetzt. Mykobacterium tuberculosis wurde in 19 (82,6%) nachgewisen. Daraus foigt, dass 1. mehrere Punktionen desselben vergrösserten Knoten durchgeführt werden müssen; 2. die Diagnose "granulomatöse Lymphadenitis die einer Tuberkulose entsprechen könnte" kann auch ohne den Nachweis säurefester Stäbchen gestellt werden; 3. PCR und andere Methoden liefern zusätzliche Informationen; 4. bei Unklarheiten hinsichtlich des klinischen Bildes wird eine offene Biopsie empfohlen.

Schlüsselworte: FNP, granulomatöse Lymphadenitis, Tuberkulose

INTRODUCTION

Lymphadenopathy, as a feature of a variety of diseases, often becomes a target for FNA cytology. In developed countries, where diseases associated with a compromised immune system are more common, cytodiagnosis of granulomatous lymphadenitis can be problematic. On the other hand, in developing countries such as Turkey, tuberculosis is still a major health problem, and FNA cytology provides an easy, quick, highly reliable and cost-effective tool for diagnosing the disease. The present study was carried out to describe cytomorphological findings of tuberculous lymphadenitis and to encourage performance of FNA cytology as a first step diagnostic method for lymphadenopathy.

MATERIALS AND METHODS

Fifty-eight patients presenting with palpable lymph nodes and with no other known diseases were referred to the FNA cytology out-patient clinic in Çukurova University Medical Faculty during a recent 40-month period. Thirty of the patients were female and 28 male, with an age range of 5–80 years.

The FNAs were performed by a pathologist (C.E.) with a 25 G needle attached to a 10-ml syringe and syringe holder (Cameco). Multiple sites were aspirated from each node. The aspirated material was smeared on two to eight slides; two or three were fixed immediately in 95% ethanol, and the remaining air-dried. Air-dried smears were stained with May–Grünwald–Giemsa (MGG) stain. If granulomatous lymphadenitis with or without caseation necrosis or purulent material was seen in these smears Ziehl–Neelsen acid fast (ZNAF) and Gomori's methenamine silver (GMS) stains were applied to wet-fixed smears. The third smear was stained with Papanicolaou stain. For this study, all the Papanicolaou-stained slides were retrieved from the archive and destained. Modified

Kinyoun acid-fast (MKAF) stain was applied to the destained slides, subsequently[1]. A control smear obtained from tuberculous culture media was stained simultaneously. In 19 cases in which subsequent open biopsy was performed, routine histological sections from formalin-fixed, paraffin-embedded material were stained with haematoxylin and eosin (H–E), ZNAF, MKAF, and GMS.

FNA cytology smears of 10 cases with granulomatous lymphadenitis, nine cases with granulomatous lymphadenitis and caseation necrosis, and four cases with caseation necrosis were sent to the Department of Microbiology for polymerase chain reaction (PCR) testing. PCR amplification was also applied to histological sections of six cases in which the diagnoses were consistent with their FNA cytology counterparts. PCR amplification was performed according to the technique described in the literature in order to demonstrate *Mycobacterium tuberculosis*[2–4].

RESULTS

A total of 40 cervical, 11 submandibular, six supraclavicular, three submental, two axillar and one suboccipital FNA cytology samples were obtained from 58 patients. The cytologic diagnoses of 63 FNA cytology samples are summarized in Table 1. The cytologic and histological diagnoses of 19 cases which underwent subsequent open biopsy after FNA cytology are shown in Table 2.

Table 1. Cytologic diagnosis of 63 FNA cytology samples

Cytologic diagnosis	No. of cases	%
Granulomatous lymphadenitis with caseation necrosis	9	14.28
Granulomatous lymphadenitis without caseation necrosis	16	25.39
Caseation necrosis	7	11.11
Reactive hyperplasia	14	22.22
Suppurative/purulent inflammation	7	11.11
Metastatic carcinoma	6	9.52
Hodgkin's lymphoma	2	3.17
Non-Hodgkin's lymphoma	2	3.17

Table 2. Cytologic and histological diagnosis of 19 cases with open biopsy

	GLCN	GL	CN	RH	MC	HL	NHL
Histological diagnosis consistent with FNA cytology	2	3	3	3	3	1	1
Histological diagnosis not consistent with FNA cytology		1		1			1

GLCN, Granulomatous lymphadenitis with caseation necrosis; GL, granulomatous lymphadenitis; CN, caseation necrosis; RH, reactive hyperplasia; MC, metastatic carcinoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma.

Smears revealing granulomatous lymphadenitis with caseation necrosis or caseation necrosis only were considered as tuberculous lymphadenitis (16 cases, 25%). Sixteen cases were granulomatous lymphadenitis without caseation necrosis (25%). The most characteristic morphological features among these cases were epithelioid cell clusters with or without caseation necrosis (20 cases, 62.5%); Langhan's multinucleated giant cells were observed in nine of these cases. The typical epithelioid cells had elongated or foot-print shaped, pale nuclei and finely granular cytoplasm (Figure 1). When the clusters were thick or highly cellular, careful observation of the periphery of the clusters helped to find easily recognizable epithelioid cells detached from the cell cluster during smearing (Figure 2). Langhan's giant cells appeared as large cells with many nuclei, usually arranged at the periphery of the copious cytoplasm. Caseation necrosis revealed a typical macroscopic appearance with yellowish white, coarsely granular material, and during smearing it gave an impression of mashing white Turkish cheese. Microscopically, this material revealed clumps of pink acellular debris reminiscent of dry soil (Figure 3).

ZNAF and MKAF stains were negative in all FNA cytology smears and in histological sections of 19 tuberculous lymphadenitis cases. No fungal structures were seen on GMS staining.

PCR amplification demonstrated *M. tuberculosis* in eight of nine cases with granulomatous lymphadenitis with caseation necrosis, eight of 10 cases with granulomatous lymphadenitis without caseation necrosis, and three of four cases which revealed only caseation necrosis in FNA cytology smears. Histological sections of six cases revealed *M. tuberculosis* with this technique.

DISCUSSION

Tuberculous lymphadenitis is not uncommon in developing countries, such as Turkey, India and many African countries. Therefore, an inexpensive, safe and rapid method is needed to diagnose the disease. FNA cytology not only fulfils all these criteria, but also avoids the possible physical and psychological complications of an open surgical biopsy[1,5].

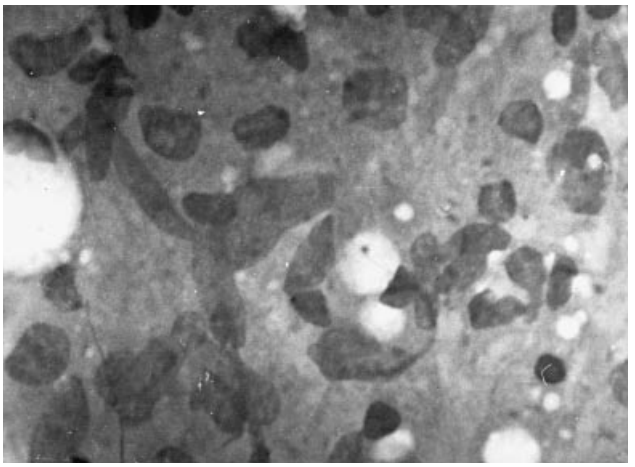

Figure 1. Epithelioid cells with elongated or foot-print shaped, pale nuclei and finely granular cytoplasm (MGG × 1000).

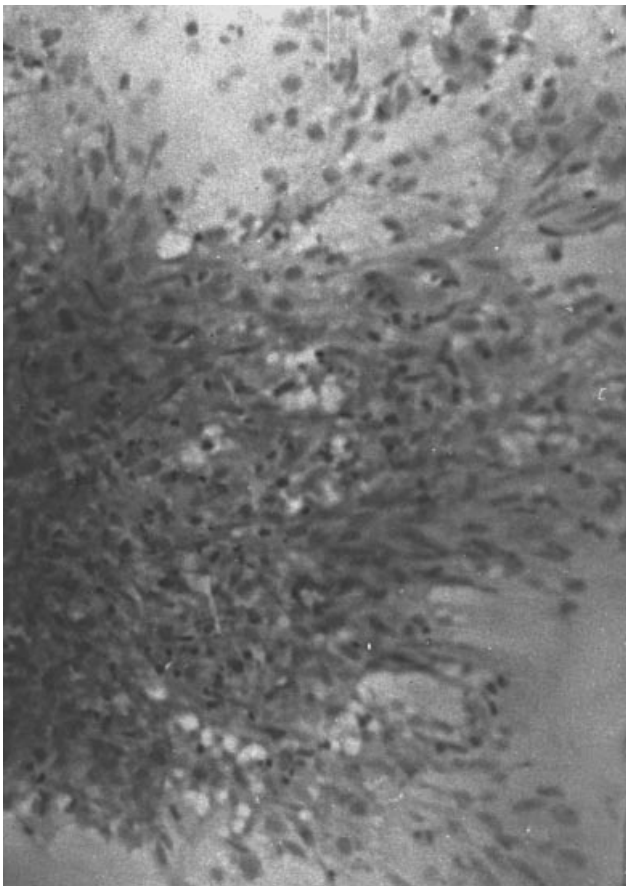

Figure 2. A thick cluster of epithelioid cells. Epithelioid cells are better seen at the periphery (Papanicolaou × 400).

In the present study, we re-examined FNA cytology smears of 32 cases of tuberculous lymphadenitis in order to define characteristic cytomorphological features. Macroscopical observation of the aspirated material during smearing gives an important clue to the cytopathologist when performing the aspiration. The caseous necrosis has a quite typical appearance of a white cheesy material. The cytodiagnosis of tuberculous lymphadenitis is straightforward when epithelioid cell clusters, Langhans' giant cells, and caseous necrosis are seen together in one smear, but sometimes only a single component is present. Therefore, it is necessary to perform at least two to three aspirations from different sites of the enlarged lymph node and to prepare several smears from each aspirate. In typical cases MGG staining provides a qualified morphologic picture; however, the Papanicolaou stain is more helpful in displaying the degenerate epithelioid cells hidden in necrotic material.

Among the FNA cytology cases of granulomatous lymphadenitis, one was misdiagnosed which was found to be Hodgkin's lymphoma with non-caseating granulomas on the histological sections[6]. We believe this could be an important diagnostic pitfall.

Our cytomorphologic features for diagnosing tuberculous lymphadenitis are similar to previous publications[7–10]. However, both ZNAF and MKAF stains failed to demonstrate acid-fast bacilli in all cytologic and histological slides, although the control smears were

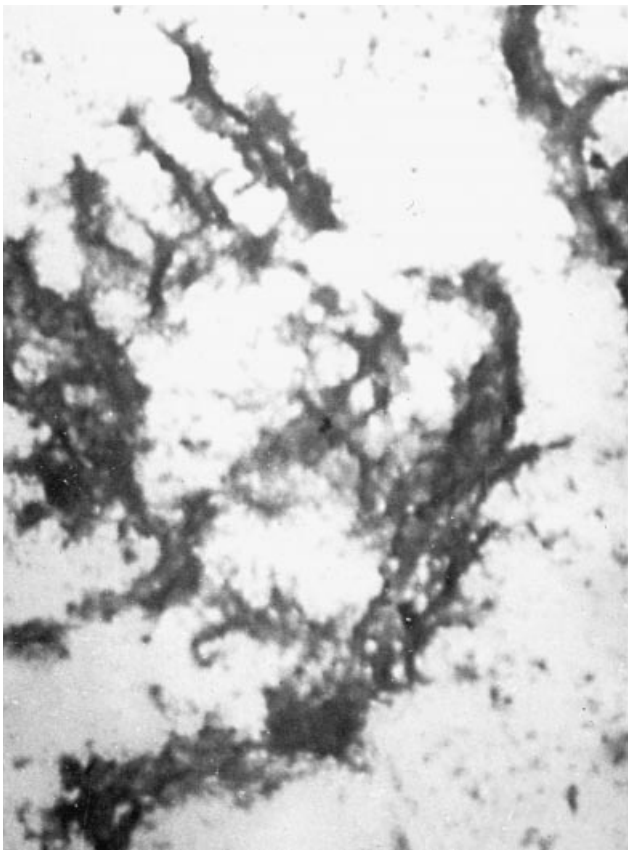

Figure 3. Caseation necrosis appearing as clumps of acellular debris reminiscent of dry soil (MGG × 400).

positive. Sadanah Metre and Jayaram reported 66% acid-fast positivity in purulent aspirates and achieved the lowest rate of positivity in cases of tuberculosis in which the aspirate was mixed with blood[8]. They suggest performing ZNAF staining on all aspirates from cases of suspected tuberculosis. In Gupta's series ZNAF staining revealed the tuberculous nature of the lesion in 11.4% of cases which would have been missed on cytology alone[5].

PCR, as a technique with a remarkable sensitivity to detect various microbiological agents, was a support for proving our FNA cytology results. On the other hand, it is expensive and requires additional time and technical equipment. Nevertheless, if available, application of the PCR amplification technique will add valuable information and give the clinician more confidence in planning and managing anti-tuberculous therapy.

We conclude that in countries with a high incidence of tuberculosis when the cytopathologist observes any cytological combination mentioned above, the diagnosis of 'granulomatous lymphadenitis, consistent with tuberculosis' can be given even though the acid-fast stains are negative. This policy will save time, money, and effort of the patient and clinician. If, however, there is a significant discrepancy with the clinical impression, or a response to anti-tuberculous therapy is not achieved, an open biopsy is recommended.

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