

Paper

Fine needle aspiration cytology (FNAC) in the diagnosis of granulomatous lymphadenitis

V Koo, TF Lioe, RAJ Spence

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ABSTRACT

Objective: To determine the final histological and clinical diagnosis of patients with granulomatous lymphadenitis on fine needle aspiration cytology (FNAC).

Method: A retrospective cohort study was carried out over a five year period in a tertiary referral hospital. FNAC of 22 patients with granulomatous lymphadenitis was reviewed and correlated with the final histological diagnosis and clinical outcome.

Results: Fourteen cases (64%) underwent surgical biopsy for histological assessment. A definitive diagnosis on FNAC with ancillary investigations was achieved in 82% (18 out of 22) of the cases: four Hodgkin's lymphoma, two non-Hodgkin's lymphoma (NHL), five tuberculosis (TB), two toxoplasmosis, one sarcoidosis and four benign reactive changes.

Conclusion: A significant number of cases of FNAC diagnosed granulomatous lymphadenitis have an identifiable underlying cause. Patients with reactive cytological changes, who clinically appear benign, can avoid unnecessary surgery.

INTRODUCTION

The use of fine needle aspiration cytology (FNAC) in the investigation of lymphadenopathy has become an acceptable and widely practised minimally invasive technique, which is safe, simple, rapid and relatively pain-free. FNAC is highly cost effective and accurate as a first line investigative technique with differential diagnoses including reactive hyperplasia/inflammatory conditions, granulomatous disorders and malignancy, stratifying cases requiring further investigations, surgical intervention or clinical follow-up. We report our experience of 22 cases of granulomatous inflammation diagnosed by FNAC.

MATERIAL AND METHODS

Patients with superficial nodes were referred to a Head and Neck clinic for physical examination and further assessment. Routine FNAC was performed by the attending pathologist. Aspiration of superficial enlarged lymph nodes was performed free hand using a 23 G needle mounted on a Cameco handle.

Both air-dried and wet-fixed slides were prepared. The air-dried smears were immediately stained with Speedy-Diff (Clin-tech) and the adequacy of diagnostic material assessed. Results of FNAC were available on the day of examination.

Granulomata are recognised cytologically by observing aggregates of histiocytes with, and

Department of Surgery, Belfast City Hospital Trust, Belfast, Northern Ireland.

V Koo, MBBCh, AFRCSI, Surgical Research Fellow.

RAJ Spence, OBE, MA, MD, FRCS, Professor and Consultant Surgeon.

Department of Cyto/Histopathology, Belfast City Hospital Trust, Belfast, Northern Ireland.

TF Lioe, MBBCh, FRCPath, Consultant Pathologist.

Correspondence to Dr TF Lioe, Department of Cyto/Histopathology, Belfast City Hospital, Lisburn Road, Belfast BT9 7AD.

E-mail: tong.lioe@bll.n-i.nhs.uk

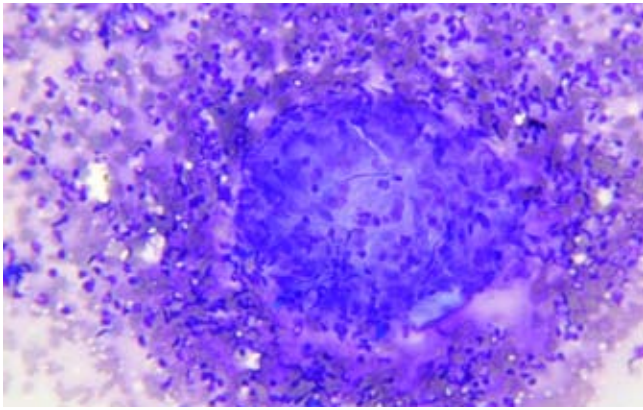


Fig 1. Granuloma formation as seen on fine needle aspirate

without, associated multinucleated giant cells. (figures 1 & 2) A dirty necrotic background would suggest caseation and possibly tuberculosis. In cases where an infective aetiology was thought likely, needle washings were sent for bacteriological culture and sensitivity. If TB was suspected, an additional sample was sent for culture and slides were also stained with auramine-rhodamine or Ziehl-Neelsen methods to detect acid fast bacilli (AFB) directly.

The eventual diagnosis of granulomatous inflammation by FNAC was confirmed either by surgery and/or by clinical investigations. In addition to cytological or histological features, patients suspected of TB had positive culture of *Mycobacterium tuberculosis*. The diagnosis of sarcoidosis was based on the generally accepted diagnostic criteria: clinical picture and chest x-ray findings compatible with sarcoidosis, elevated serum angiotensin converting enzyme (ACE) and lysozyme, skin test (Kveim and Mantoux test) and response to treatment with steroids. Patients suspected of toxoplasmosis had IgG and IgM toxoplasma antibodies assayed by micro-enzyme-linked immunosorbent assay (ELISA) method.

RESULTS

Between September 1995 and June 2001, 22 patients had the diagnosis of granulomatous inflammation made by FNAC at the Belfast City Hospital. Seven patients were male and 15 female; and the mean age of diagnosis was 54 years. All patients presented with a palpable lesion, which was usually enlarged cervical lymph nodes (n=19) or nodes elsewhere [in breast and axilla] (n=3). Fourteen out of 22 (64%) had their diagnosis confirmed through histological assessment. The eventual diagnoses based on surgical biopsy and clinical investigations were as follows: four cases of Hodgkin's disease, two cases NHL,

five cases of TB, two cases of toxoplasmosis, one of sarcoidosis, four of benign/reactive and four unknown.

MALIGNANT LYMPHOMA

Six cases (20%) were reported as malignant lymphoma: four Hodgkin's disease and two NHL (one B-cell, one T-cell lymphoma). All six cases had the diagnosis confirmed by excisional biopsy. One patient was previously diagnosed with Lennert's T-cell lymphoma and had a recurrence of disease one year later, proven on FNA cytology of cervical lymphadenopathy. This patient subsequently moved to Scotland to have further treatment and follow up. The other five patients were diagnosed primarily on FNA. FNA suggested features of lymphoma, and in four patients surgical excision biopsy was undertaken which confirmed the diagnosis of malignant lymphoma. These four patients underwent chemotherapy and have remained well. One of them returned to his home in Scotland to have further follow-up and treatment.

INFECTIVE AGENTS

Four of the five patients diagnosed with tuberculous lymphadenitis on FNA presented with enlarged lymph nodes as the only clinical finding. All cases responded well to anti-tuberculous therapy. One of them was a student from the Indian subcontinent and aspirate culture for *Mycobacterium tuberculosis* was positive. Another patient was a 33 year old lady from China with recurrent neck lymphadenopathy which started discharging milky fluid that grew TB on aspirate culture. Another patient had no previous BCG vaccination and had been consuming un-pasteurised milk shortly before symptomatic presentation. In all cases, FNA aspirates cultured positive for TB.

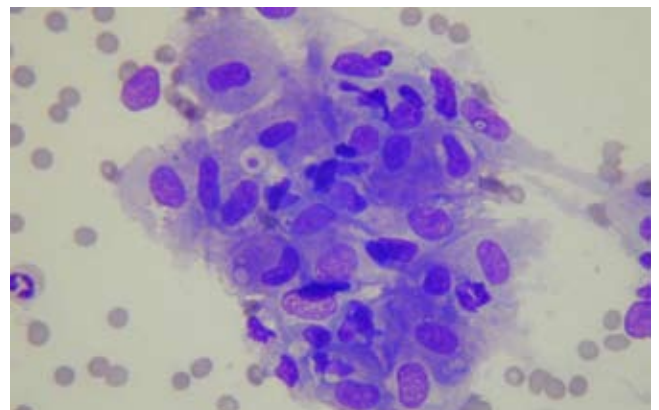


Fig 2. Granuloma-loose aggregates of epithelioid histiocytes

The two cases of toxoplasmosis, had the typical FNAC features including presence of follicular hyperplasia with secondary germinal centres rich in macrophages, presence of groups of epithelioid cells and presence of monocytoïd histiocytes,^{21,22} the diagnosis was confirmed with positive IgG and IgM antibody titres. The lymphadenopathy in both patients disappeared during their follow-up, and both have remained asymptomatic.

SARCOIDOSIS

One patient was diagnosed with sarcoidosis in our series. The patient was previously diagnosed with sarcoidosis following positive ACE level, Kveim-Stilzbachs test and Mantoux test one year previously. The FNA of lymph node findings were characteristic, with epithelioid non-caseating granuloma and occasional multi-nucleated giant cells. The patient was started on a course of steroid to which she had a good response. (after five days, her lymphadenopathy disappeared).

UNKNOWN CAUSE

In four patients, the precise cause for the granulomatous inflammation was not established. Of these, three patients were clinically unfit for surgical excisional biopsy due to severe co-morbid factors and the ancillary tests did not reveal any obvious cause. All three patients subsequently died of causes unrelated to granulomatous lymphadenitis. One patient refused further follow-up and investigation and decided to discharge herself against medical advice.

BENIGN/REACTIVE CAUSE

In four patients, the ancillary clinical investigations and excisional biopsies were reactive. On clinical follow-up in these patients, the lymphadenopathy had disappeared and the patients have remained well and have subsequently been discharged.

DISCUSSION

The well-defined role of FNAC in the investigation of lymphadenopathy has previously been studied.^{1,2} In the context of granulomatous disorders, the possible aetiology is wide and the use of FNAC with other ancillary tests (microbiological, immunohistochemical, radiological, biochemical and special staining techniques) is useful for obtaining a definitive diagnosis. The algorithm shows a useful classification of the aetiology of granulomatous lymphadenopathy.

FNAC as a first line screening method has been recommended in suspected malignancy.^{2,3} The presence of granulomata in an aspirate may indicate the presence of a neoplastic process. The background cell population needs to be scrutinised if a malignant lymphoma is suspected. Granulomata may be encountered in both Hodgkin's disease and non-Hodgkin's lymphoma, particularly T-cell lymphoma.⁴ Hodgkin's lymphoma is characterised by the classic Reed-Sternberg cells in a background of sarcoid-like granulomata, reactive lymphoid cells and occasional eosinophils.^{5,6,7} Occasionally, lymph nodes containing metastatic carcinoma may also show features of granulomata. Previous reports have been described in metastatic nasopharyngeal carcinoma, seminoma and malignant melanoma.^{8,9} Histologically, non-caseating granulomata composed of epithelioid histiocytes with multinucleated giant cells are seen, but these can be indistinguishable from granulomatous inflammation from other causes. A series by Khurana *et al*¹⁰ highlighted the difficulties encountered in making a definitive diagnosis of malignant neoplasm that mimics, or occurs, in association with granulomata.

Granulomatous inflammation found in lymph nodes draining carcinomas is a recognised phenomenon.^{10,11,12} Such phenomenon are reported in pulmonary small cell carcinoma,¹³ malignant melanoma,⁹ papillary thyroid carcinoma,¹⁴ gastric carcinoma,¹⁵ and rhabdomyosarcoma.¹⁶ This has been suggested to be either a response to necrotic material¹² or an immunological T-cell mediated hypersensitivity reaction to cell surface antigens.^{17,18,19} However, the precise mechanism is largely speculative as the exact tumour or host factors that enable such a response remain unknown. We agree with Lui *et al*²⁰ in their pragmatic approach of diligent examination of FNAC slides combined with ancillary clinical, serological and imaging investigations in the drainage areas to identify any occult malignancy.

A suspicious clinical history of TB (pyrexia, night sweats, recent travel to endemic areas, no previous BCG vaccination) coupled with positive aspirate, blood, sputum or urine tests for AFB and good response to anti-tuberculous therapy supports the diagnosis of TB. One disadvantage is the inherent delay in culture result, but it is anticipated that as polymerase chain reaction and other amplification techniques become more common, detection time for the organism will shorten, improving the value of FNA in clinical practice.²¹ The typical FNAC features

of toxoplasmosis include the presence of follicular hyperplasia with secondary germinal centres rich in macrophages, presence of groups of epithelioid cells and presence of monocytoïd histiocytes have been previously described.^{22,23} A combination of FNA features with positive serological testing and history of animal contact, as in the two patients here, gives the diagnosis of toxoplasmosis and thus avoids unnecessary surgical excision.

Sarcoidosis is a disease of unknown aetiology that can be characterised by the histological hallmark of epithelioid non-caseating granulomas, usually accompanied by multinucleated giant cells. The World Association and Other Granulomatous Diseases (WASOG) diagnostic criteria for sarcoidosis include that granulomata present in two or more organs with no agent known to cause a granulomatous response identified.²⁴ Although

there is no single gold standard test, the important role of FNAC in histological diagnosis and its underutilisation was highlighted by Tambouret *et al.*²⁵ We agree with the authors that FNAC used in conjunction with clinical findings, radiological and laboratory investigations can be a cost effective method.

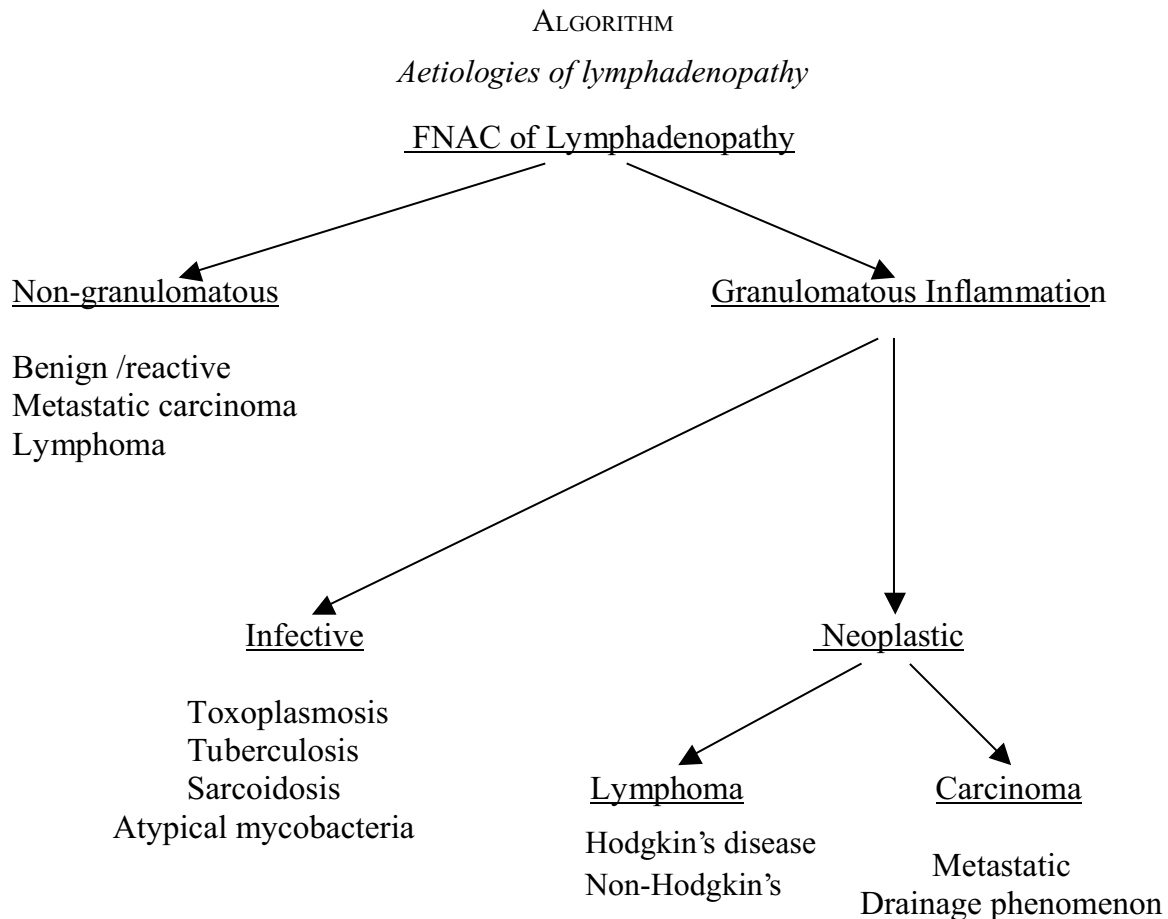
CONCLUSION

A significant number of cases of FNAC diagnosed granulomatous lymphadenitis have an identifiable underlying causal pathology. Our experience suggests that FNAC combined with clinical correlation is useful as a first line investigation. The high specificity of the technique helps to single out those that need further investigation or biopsy. It is also highly cost effective in the diagnosis of relapse in patients with malignancies.

TABLE

Biopsy site, histological and clinical diagnosis of 22 patients with FNA cytologically diagnosed granulomatous lymphadenitis.

No	Sex	Age	FNA Site	Histology	Clinical diagnosis
1	F	91	Neck	Not done	Unknown
2	F	67	Neck	Granulomatous lymphadenitis	Unknown
3	F	40	Breast	Not done	Unknown
4	F	84	Neck	Not done	Unknown
5	F	52	Neck	Not done	Benign reactive
6	F	86	Neck	Granulomatous lymphadenitis	Benign reactive
7	F	36	Neck	Granulomatous lymphadenitis	Benign reactive
8	F	22	Breast	Granulomatous lymphadenitis	Benign reactive
9	M	60	Axilla	Hodgkin's	Hodgkin's
10	M	43	Neck	Not done	Hodgkin's
11	M	77	Neck	Hodgkin's	Hodgkin's
12	M	17	Neck	Hodgkin's	Hodgkin's
13	M	85	Neck	NHL	NHL
14	F	61	Neck	NHL	NHL
15	F	39	Neck	Granulomatous lymphadenitis	Sarcoidosis
16	F	65	Neck	Granulomatous lymphadenitis	TB
17	F	69	Neck	Granulomatous lymphadenitis	TB
18	F	48	Neck	Granulomatous lymphadenitis	TB
19	F	33	Neck	Not done	TB
20	M	33	Neck	Not done	TB
21	F	60	Neck	Granulomatous lymphadenitis	Toxoplasmosis
22	M	27	Neck	Not done	Toxoplasmosis



REFERENCES

1. Steel BL, Schwart MR, Ramzy I. Fine needle aspiration biopsy in the diagnosis of lymphadenopathy in 1103 patients. Role, limitations and analysis of diagnostic pitfalls. *Acta Cytol* 1995; **39(1)**: 76-81.
2. Lioe TF, Elliott H, Allen DC, Spence RA. The role of fine needle aspiration cytology (FNAC) in the investigation of superficial lymphadenopathy; uses and limitations of the technique. *Cytopathol* 1998; **10(5)**: 291-7.
3. Klemi PJ, Elo JJ, Joensuu H. Fine needle aspiration biopsy in granulomatous disorders. *Sarcoidosis* 1987; **4(1)**: 38-41.
4. Schneider DR, Taylor CR, Parker JW, Cramer AC, Meyer PR, Lukes RJ. Immunoblastic sarcoma of T- and B- cell types: morphologic description and comparison. *Hum Pathol* 1985; **16(5)**: 885-900.
5. Friedman M, Kim U, Shimaoka K, Panahon A, Han T, Stutzman L. Appraisal of aspiration cytology in management of Hodgkin's disease. *Cancer* 1980; **45(7)**: 1653-63.
6. Kardos TF, Vinson JH, Behm FG, Frable WJ, O'Dowd GJ. Hodgkin's disease: diagnosis by fine-needle aspiration biopsy. Analysis of cytologic criteria from a selected series. *Am J Clin Pathol* 1986; **86(3)**: 286-91.
7. Das DK, Gupta SK, Datta BN, Sharma SC. Fine needle aspiration cytodiagnosis of Hodgkin's disease and its subtypes. I. Scope and limitations. *Acta Cytol* 1990; **34(3)**: 329-36.
8. Blackshaw A. Metastatic tumour in lymph nodes. In: Standfield AG, D'Ardenne, editors. *Lymph node biopsy interpretation*. London: Churchill Livingstone, 1987: 380-397.
9. Coyne JD, Banerjee SS, Menasche LP, Mene A. Granulomatous lymphadenitis associated with metastatic malignant melanoma. *Histopathol* 1996; **28(5)**: 470-2.
10. Khurana KK, Stanley MW, Powers CN, Pitman MB. Aspiration cytology of malignant neoplasms associated with granulomas and granuloma-like features: diagnostic dilemmas. *Cancer* 1998; **84(2)**: 84-91.
11. Gregori HB, Othersen HB, Moore MP. The significance of sarcoid-like lesions in association with malignant neoplasm. *Am J Surg* 1962; **104**: 577-586.
12. Oberman H. Invasive carcinoma of the breast with granulomatous response. *Am J Clin Pathol* 1987; **88(6)**: 718-21.
13. Kamiyoshihara M, Hirai T, Kawashima O, Ishikawa S, Morishita Y. Pulmonary small cell carcinoma associated with sarcoid reactions: report of a case. *Surg Today* 1999; **29**: 382-4.
14. Yamauchi M, Inoue D, Fukunaga Y, Kakudo K, Koshiyama H. A case of sarcoid reaction associated with papillary thyroid carcinoma. *Thyroid* 1997; **7(6)**: 901-3.
15. Kojima M, Nakamura S, Fugisaki M, Hirahata S, Hasegawa H, Maeda D, et al. Sarcoid-like reaction in the regional lymph nodes and spleen in gastric carcinoma: a clinicopathologic study of five cases. *Gen Diagn Pathol* 1997; **142(5-6)**: 347-52.
16. Sumiyoshi A, Sannoe Y, Tanaka K. Rhabdomyosarcoma of the esophagus – a case report with sarcoid-like lesions in its draining lymph nodes and the spleen. *Acta Pathol Jpn* 1972; **22(3)**: 581-9.
17. Santini D, Pasquinelli G, Alberghini M, Martinelli GN, Taffurelli M. Invasive breast carcinoma with granulomatous response and deposition of unusual amyloid. *J Clin Pathol* 1992; **45(10)**: 885-8.
18. Coyne JD. Colonic carcinoma with granulomatous (sarcoid) reaction. *J Clin Pathol* 2002; **55(9)**: 708-9.

19. Brincker H. Sarcoid reaction in malignant tumors. *Cancer Treat Rev* 1986; **13(3)**: 467-73.
20. Lui PC, Chow LT, Tsang RK, Chan AB, Tse GM. Fine needle aspiration cytology of lymph node with metastatic undifferentiated carcinoma and granulomatous (sarcoid-like) reaction. *Pathology* 2004; **36(3)**: 273-4.
21. Ellison E, Lapuerta P, Martin SE. Fine needle aspiration diagnosis of mycobacterial lymphadenitis. Sensitivity and predictive value in United States. *Acta Cytol* 1999; **43(2)**: 153-7.
22. Putschar WG. Can toxoplasmic lymphadenitis be diagnosed histologically? *N Engl J Med* 1973; **289**: 913-4.
23. Saxen E, Saxen L, Gronross P. Glandular toxoplasmosis: A report on 23 histologically diagnosed cases. *Acta Pathol Microbiol Scand* 1958; **44**: 319-328.
24. Yamamoto M, Sharma OP, Hosado Y. Special report: the 1991 descriptive definition of sarcoidosis. *Sarcoidosis* 1992; **9**: S33-S34.
25. Tambouret R, Geisinger KR, Power CN, Khurana KK, Silverman JF, Bardales R., et al. The clinical application and cost analysis of fine-needle aspiration biopsy in the diagnosis of mass lesion in sarcoidosis. *Chest* 2000; **117(4)**: 1004-11.



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