

LYMPHADENOPATHY DUE TO TOXOPLASMOSIS

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MANY SEROLOGICAL surveys using the dye test of Sabin and Feldman (1948) have shown infection with *Toxoplasma gondii* to be widespread. It occurs with various degrees of frequency in different geographic areas and antibodies have been found in man and many species of animals (Feldman and Miller, 1956; Beattie, 1957; Jacobs, Remington and Melton, 1960; Ludlam and Beattie, 1963).

As an infection producing clinical symptoms the disease appears to be rare and the best known and longest recognised form in man in the congenital disease to which attention was drawn in 1939 by Wolf, Cowan and Paige. The acquired infection is rarely severe but a manifestation recognised with increasing frequency is lymphadenopathy, which may or may not be associated with mild constitutional symptoms. It is not unusual for the lymphadenopathy to persist for several months and this may raise the suspicion of disease of a more serious nature and result in lymph node biopsy.

The histological appearances in the lymph nodes are distinctive, although the specificity of the morphology is at present uncertain (Harrison, 1966). However, Saxen, Saxen and Gronroos (1958), Saxen and Saxen (1959) and Saxen, Saxen and Tenhunen (1962) have reported several series in Finland and stressed the diagnostic significance of the changes, and Tenhunen (1964) wrote that the histology of the lymph nodes established the correct diagnosis in over 90 per cent of cases. The importance of diagnosis lies in the differentiation of toxoplasmic lymphadenitis from malignant reticuloses, especially Hodgkin's disease (Saxen et al, 1962) and specific infections. The histology does appear to be uniform and will often allow of a provisional diagnosis which may be confirmed by serological testing for antibodies.

The present series of 6 cases has been collected on a histological basis from a routine biopsy service over a fifteen-month period. During this time a total of 340 lymph node biopsies was received giving an incidence of 1.8 per cent. They were drawn from both urban and rural populations in Northern Ireland. The biopsies were undertaken for persistent, unexplained lymphadenopathy and in only one case was toxoplasmosis considered.

HISTOLOGY

The histological changes in all six lymph nodes are very similar, although they vary in degree and the cases have been collected on the basis of the morphology.

The lymph nodes are moderately enlarged, but the architecture is preserved. There is a striking degree of follicular hyperplasia and the large follicles with active germinal centres are scattered throughout the node and vary considerably in size. The follicles are well demarcated except where the margins are interrupted by small clusters of histiocytic cells. In the reaction centres there are numerous mitotic figures and macrophages containing nuclear debris are usually abundant. There is often a marked degree of periadenitis associated with fibrous thickening of the

capsule. Many of these features, however, are common to non-specific reactive changes in lymph nodes. The more distinctive morphology is the presence of small clusters of histiocytic cells with abundant eosinophilic cytoplasm. These are scattered throughout the node both in the medulla and also in the reaction centres of the follicles (Fig. 1). These cells resemble those seen in the granulomata of Boeck's sarcoidosis and tuberculosis. There is, however, no caseation and the cell clusters

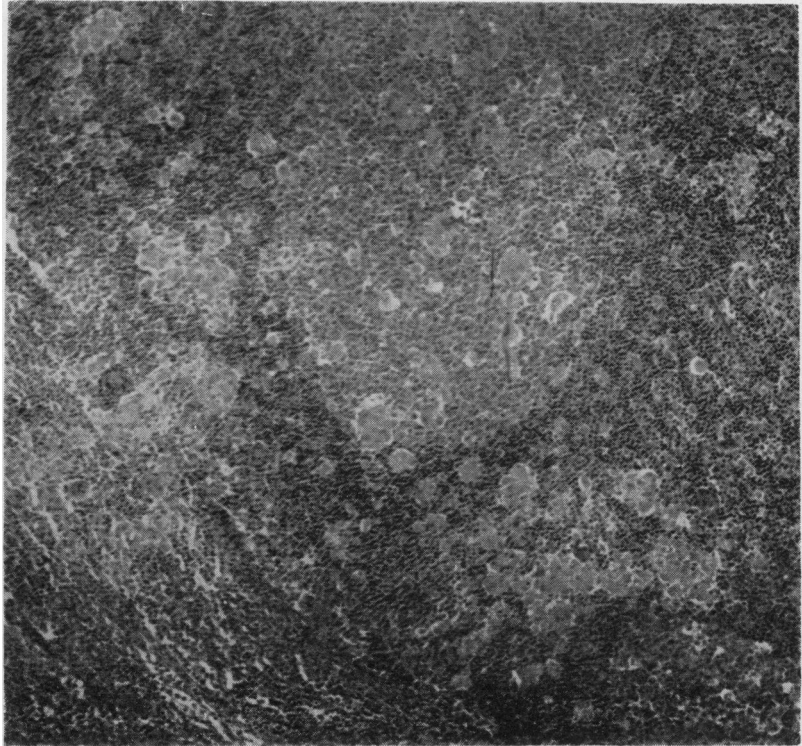


FIG. 1. Clusters of histiocytic cells in medulla and also in an enlarged follicle. *Haematoxylin and eosin x 100.*

are smaller than those usually seen in Boeck's sarcoidosis and are without giant cells. In addition in some of the nodes peripheral sinuses packed with mononuclear cells are a striking feature (Fig. 2). Many of these cells are lymphocytes but others are probably macrophages. The cell clusters of histiocytic cells and the prominent peripheral sinuses packed with mononuclear cells, when associated with marked reactive hyperplasia, are the features which suggest toxoplasmosis and remove the diagnosis from the non-specific group. There may be some variation in the extent to which the lymph nodes exhibit these changes; in some nodes the clusters of histiocytic cells are less prominent than in others but they still show the unusual pattern of distribution in the follicles. In none of the lymph nodes studied was there any infiltration by eosinophils. No toxoplasmic cysts were identified despite prolonged searching but these have only very rarely been described in lymph nodes.

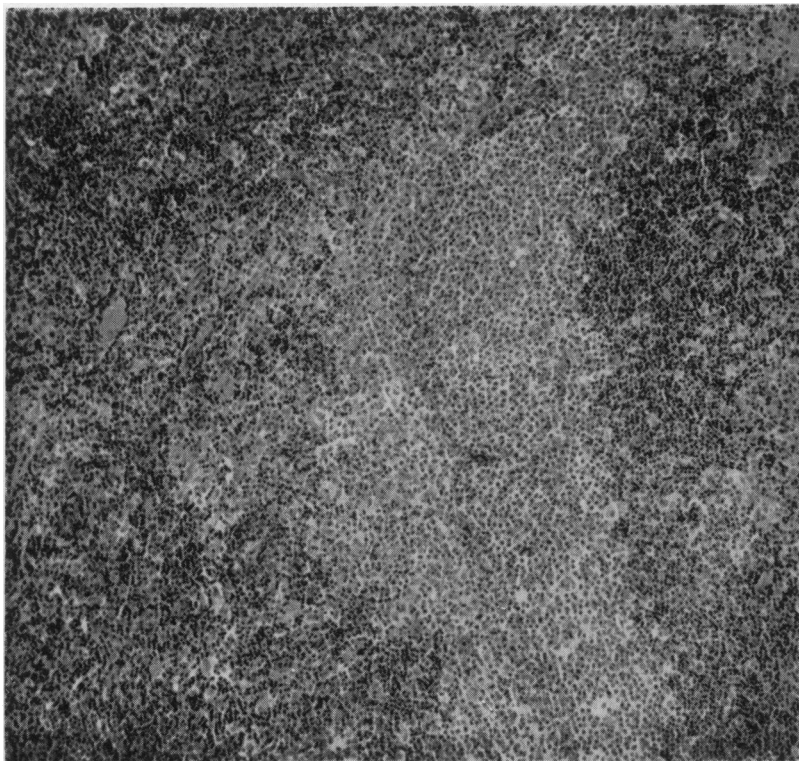


FIG. 2. *Peripheral lymph sinus packed with mononuclear cells.
Haematoxylin and eosin x 100.*

PAS positive debris may be identified in the macrophages in the germinal centres. This has been interpreted as toxoplasma organisms but the similarity to nuclear debris makes this unlikely and these appearances cannot be accepted as having any diagnostic significance.

DISCUSSION

Lymphadenopathy may clinically be a very non-specific finding and toxoplasmosis is only one of many conditions causing the enlargement. In the cases recognised in the routine biopsy service the infection was not associated with any characteristic clinical findings and persistence of the lymphadenopathy resulted in biopsy usually to exclude malignancy or tuberculosis. It has been estimated that toxoplasmosis accounts for 2 to 13 per cent of otherwise unexplained lymphadenitis (Siim, 1956, 1961; Beverley and Beattie, 1958; Saxen and Saxen, 1959; Turunen, 1963). In a series of 958 lymph node biopsies in Finland reported by Turunen (1963) toxoplasmosis was diagnosed histologically in 2.3 per cent while a higher figure of 13 per cent was found in a serological investigation of patients with lymphadenitis of uncertain aetiology (Siim, 1961). During the time the six lymph nodes in this series were recognised, a total number of 340 lymph node biopsies were received giving an incidence of 1.8 per cent. This is probably comparable with the incidence

recorded in Finland by Turunen (1963). His series consisted only of peripheral lymph node biopsies mainly from the cervical region while in this material peripheral lymph nodes from other sites and the mesentery were also included.

Toxoplasmic lymphadenitis is probably more prevalent than previously suspected and the incidence of infection obtained histologically is almost certainly low. In many cases the lymphadenopathy is transitory and does not lead to biopsy and unless the infection is suspected and antibodies looked for the aetiology remains unsuspected. The serology will often remain positive at a high titre for a considerable time after the lymph node enlargement has subsided.

The six lymph nodes all showed very similar histology but with some variation in degree and it is felt they allow a high degree of accuracy in diagnosis. While at present it is uncertain how specific these changes are for toxoplasmosis there is without doubt a striking degree of uniformity in the histology and once appreciated further cases are unlikely to escape detection. This morphology was described in 1947 by Robb-Smith and in 1952 by Piringer-Kuchinka without recognition of its aetiology. Robb-Smith (1947) described the lymph node changes as lympho-histiocytic medullary reticulosis. Later the same author, quoted by Beverley and Beattie (1958) for whom he reviewed a series of lymph nodes, doubted whether the appearances could be regarded as specific for toxoplasmosis. The diagnostic value of histological study was, however, stressed by Saxen and Saxen (1959) and Saxen et al (1962). They believed the appearances were adequate to establish the diagnosis in over 90 per cent of cases. Recently (Harrison, 1966) discussed the morphology and considered that the appearances were sufficiently characteristic to justify a provisional diagnosis pending serological investigation. Certainly in the six cases described here the small histiocytic clusters immediately attracted attention and their unusual distribution within the reacting follicles of the lymph node was striking. It is as yet uncertain how specific the histology is and the possibility of confusion with a malignant lymphoma, such as Hodgkin's disease cannot be completely excluded. The extent to which these changes occur in the lymph nodes is variable and it is possible that not all lymph nodes in toxoplasmosis show these distinctive features to draw attention to the infection. To date I have not seen any condition in which the histology has mimicked toxoplasmosis closely enough to cause confusion and all cases have been confirmed by serological tests.

Toxoplasma cysts have only very rarely been found in lymph node sections (Stanton and Pinkerton, 1953; Stansfeld, 1961). Cysts are probably the only form which should be definitely identified in tissue section. The parasite may be isolated by animal inoculation methods but this is not always possible and the diagnosis must be suspected prior to fixation of the excised lymph node.

Clinically the infection is unlikely to be diagnosed. Beverley and Beattie (1958) from a study of case records were unable to find any characteristic clinical features suggesting toxoplasmosis. Occasionally haematological investigations may be useful. In the peripheral blood there may be a relative or absolute lymphocytosis with occasional abnormal mononuclear cells similar to those seen in infectious mononucleosis (Table). The Paul-Bunnell test, however, is negative and this association is suggestive of toxoplasmosis.

Serological results provide the most useful confirmatory evidence of infection. In a disease where subclinical infection is common positive results with the dye

CLINICAL MATERIAL

<i>No.</i>	<i>Sex</i>	<i>Age</i>	<i>Site of lymphadenopathy</i>	<i>Duration of lymphadenopathy (weeks)</i>	<i>Dye test titre</i>	<i>Leucocytes/cu. mm.</i>	<i>Lymphocytes cu. mm.</i>
1	F	27	Cervical	5	1/512	6,700	2412
2	F	21	Cervical	12	1/8192	3,700	2072
3	M	10	Axillary	11	1/4096	8,900	2248
4	F	23	Cervical	7	1/4096	4,000	2240
5	M	7	Axillary	—	1/2048	—	—
6	F	37	Cervical	8	1/128,000	5,000	2050

test are to be expected and may only indicate that the patient has been infected at some time with the organism. The titre in the glandular form of the disease is strongly positive as would be expected with a recent acquired infection and in conjunction with the histology gives reliable evidence of toxoplasmosis. From the table it can be seen that 5 of the 6 cases had strong serological reactions with titres above 1 in 2,048. In case 1 the titre was 1 in 516. Harrison (1966) considers that the titre must be in the order of 1 in 250 to make a diagnosis, but a higher titre is probably desirable. This level of dye test antibodies was found by Beattie (1957) in 0.2 per cent of a normal population and he believes that it is not unreasonable to look for a titre of 1 in 1,000, especially in the absence of the more reliable evidence provided by a rising titre (Beattie, 1967). This has also been emphasised as a feature of glandular toxoplasmosis in Scandinavia (Saxen et al, 1962). Case 1 had the shortest history of lymphadenopathy and it is quite possible that a higher titre might have been obtained with further testing at a later date. The antibody dye test may take up to 3 months to rise to a maximum titre (Saxen, Saxen and Gronroos, 1958; Tenhunen, 1964) and low titres in the early stages of infection may be misleading and do not exclude toxoplasmosis. Repeated low antibody reactions would certainly indicate the need for the histology of the lymph nodes to be reassessed.

SYNOPSIS

Six cases of acquired toxoplasmic lymphadenopathy are described involving peripheral lymph nodes. This gives an incidence of 1.8 per cent in a total of 340 lymph node biopsies received in a routine biopsy service over a period of fifteen months. The service covers rural and urban populations in Northern Ireland. Toxoplasmosis appears to be a commoner cause of lymphadenopathy than previously suspected.

The infection has been recognised on the basis of histological criteria and the distinctive changes in the lymph nodes are described. They allow a presumptive diagnosis of toxoplasmic lymphadenitis to be made.

The value of confirmatory serological tests is stressed and the high antibody dye test titres obtained are a typical feature of the disease without which the diagnosis is not justified.

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REFERENCES

- BEATTIE, C. P. (1957). *Trans. roy. Soc. trop. Med. Hyg.*, **51**, 96.
BEATTIE, C. P. (1967). *Recent Advances in Medical Microbiology*, p. 339, Churchill, London.
BEVERLEY, J. K. A., and BEATTIE, C. P. (1958). *Lancet*, **2**, 379.
FELDMAN, H. A., and MILLER, L. T. (1956). *Amer. J. Hyg.*, **64**, 320.
HARRISON, C. V. (1966). *Recent Advances in Pathology*, Eighth Edition, p. 207, Churchill, London.
JACOBS, L., REMINGTON, J. S. and MELTON, M. L. (1960). *J. Parasitol.*, **46**, 23.
LUDLAM, G. B. and BEATTIE, C. P. (1963). *Lancet*, **2**, 1130.
PIRINGER-KUCHINKA, A. (1952). *Verh. dtsch. Ges. Path.*, **36**, 352.
ROBB-SMITH, A. T. H. (1947). *Recent Advances in Clinical Pathology*, p. 355, Churchill, London.
SABIN, A. B. and FELDMAN, H. A. (1948). *Science*, **108**, 660.
SAXEN, E. and SAXEN, L. (1959). *Lab. Invest.*, **8**, 386.
SAXEN, E., SAXEN, L. and GRONROOS, P. (1958). *Acta. path. microbiol. scand.*, **44**, 319.
SAXEN, E., SAXEN, L. and TENHUNEN, A. (1962). *Acta. path. microbiol. scand.*, **56**, 284.
SIIM, J. C. (1956). *Ann. N.Y. Acad. Sci.*, **64**, 185.
SIIM, J. C. (1961). *Survey. Ophthal.*, **6**, 781.
STANSFELD, A. G. (1961). *J. clin. Path.*, **14**, 565.
STANTON, M. F. and PINKERTON, H. (1953). *Amer. J. clin. Path.*, **23**, 1199.
TENHUNEN, A. (1964). *Acta. path. microbiol. scand.*, suppl. **172**.
TURUNEN, M. (1963). *Acta. chir. scand.*, **126**, 53.
WOLF, A., COWAN, D., and PAIGE, B. H. (1939). *Science*, **89**, 226.

BOOK REVIEW

THE POCKET PRESCRIBER AND GUIDE TO PRESCRIPTION WRITING.

By A. G. Cruikshank, F.R.C.P.Ed. Eighteenth Edition. (Pp. vii+303. 10s).
Edinburgh and London: E. & S. Livingstone, 1969.

OLD and small and quaint. The eighteenth edition of this book first published in 1882, is 7×10.6×1.4 cm. in size and weighs 90 G. It fits the smallest pocket in my waistcoat. Doses are all metric. Prescriptions and remedies are listed rather arbitrarily under disease headings – both sciatica and scurvey come under “General and Metabolic Diseases” – and I found it difficult to find what I wanted because drugs are not listed in the index.

There is a section on “Some Modern Remedies” which includes some proprietary preparations which would be better omitted and there is another section rather quaintly entitled “Selected National Formulae”: I had hoped this would contain the medical equivalent of Mrs. Beeton’s Scottish haggis and Italian risotto; it contains a selection of monographs from the British National Formulary. I think the British National Formulary is better value and easier to use than the little book. But I like the first two pages on “Some Points of Practice” and I hope the little fellow makes his centenary. O.L.W.