Necrotising lymphadenitis without granulocytic infiltration (Kikuchi’s disease)

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SUMMARY Kikuchi’s disease (necrotising lymphadenitis) is characterised by cervical lymphadenopathy in young patients and may be mistaken for malignant disease both clinically and histologically. Microscopically, there is a varying degree of effacement of the lymph node architecture and necrosis with an infiltrate of “histiocytic” cells and absence of polymorphs. The disease is of unknown aetiology. It was originally described in Japan, and only 27 cases have been reported elsewhere (none in the United Kingdom), although it has probably been seen but not recognised. The clinical, histopathological, electron microscopic, and immunohistological findings in four cases of the disease were evaluated.

In 1972 Kikuchi1 and Fujimoto et al2 described an unusual lymphadenitis which they called “lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytosis,” and “cervical subacute necrotising lymphadenitis,” respectively. In the wake of this many examples of this lesion were described but only in Japanese patients.3-11 The terms used varied—necrotising histiocytic lymphadenitis, necrotising lymphadenitis, phagocytic necrotising lymphadenitis, and pseudolymphomatous hyperplasia—but all the reports emphasised the necrotic changes characteristically seen in the nodes and commented on the apparently “histiocytic” infiltrate bordering the necrotic areas. More recently, Pileri et al reported the lesion outside Japan for the first time and termed it “histiocytic necrotising lymphadenitis without granulocytic infiltration”12 and Ferrer et al reported three cases that had been analysed using cell marker studies.13

We now report four more cases of this distinctive lymphadenitis in the United Kingdom, with some immunohistological and ultrastructural studies. We wish to draw attention to the condition and its histopathological differential diagnosis and to comment on the changes in the lymph nodes that we observed.

Material and methods

The tissue from four lymph nodes was fixed in 10% buffered formaldehyde, processed for routine light microscopy, sectioned at 5 µm, and stained with haematoxylin and eosin, methyl green pyronin, Giemsa, and reticulin. Immunoperoxidase studies were carried out on two cases using the peroxidase-antiperoxidase technique for lysozyme and α1-antitrypsin and immunoglobulins. For electron microscopy tissue embedded in paraffin and fixed in formalin was retrieved from two cases, and ultra thin sections were prepared in Epon and viewed in a Phillips electron microscope 400. The medical records of all four patients were reviewed.

CASE REPORTS

Case 1 A 29 year old Asian woman presented with an enlarged lymph node in the left cervical region present for six months and which had become painful four weeks before it was biopsied. She had symmetrically enlarged lymph nodes in both axillae, which were firm. The presumptive diagnosis was either lymphoma or tuberculosis. Investigations showed: erythrocyte sedimentation rate 10 mm in the first hour, white cell count 3.2 × 10⁹/l (neutrophils 38%, lymphocytes 54%, macrophages 4%, indicative of leucopenia). The left cervical lymph node was biopsied and cultured. No viruses, acid fast bacilli, or other bacteria were grown. She remained well with no residual lymphadenopathy after 18 months.

Case 2 A 17 year old white boy presented with a tender lump 1.5 cm in diameter below the left mandible, which had been present for about four weeks. He had no history of malaise or any other illness. No investigations were carried out, and the node was biopsied. Fourteen months later he remained well.
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**Fig. 1** Case 3: ill defined disintegrating lymphoid follicle with germinal centre. (Haematoxylin and eosin.) × 100.

**Fig. 2** Case 2: necrotic focus showing pale background and degenerate cell debris. (Haematoxylin and eosin.) × 250.

**Fig. 3** Case 2: reticulin stain of necrotic area showing preserved vessel outlines and background cortical reticulin. (Reticulin.) × 100.

**Fig. 4** Case 1: well preserved cells and degenerate pyknotic nuclear debris at edge of necrosis. Many histiocytic cells are present. (Haematoxylin and eosin.) × 600.

**Case 3** A 21 year old white woman presented with tender right cervical lymphadenopathy, which increased in size over the next 10 days. There were no other abnormal physical signs. Investigations showed: erythrocyte sedimentation rate 54 mm in the first hour, white cell count 2·5 × 10⁹/l (neutrophils 23%, lymphocytes 70%, indicative of leucopenia). Serology (toxoplasma, viral antibodies, yersinia) yielded negative results as did the Paul-Bunnell test. A node was biopsied, and cultures for viruses and bacteria, including acid fast bacilli, were negative. Eight months later she remained well; the residual lymphadenopathy had regressed completely.

**Case 4** An 18 year old black man presented with a four day history of a painful swelling under the jaw to the right of the midline, which had been getting progressively larger. It measured about 6 × 4 cm at
biopsy. Both virological and bacteriological cultures of the node yielded negative results. Investigations showed: erythrocyte sedimentation rate 2 mm in the first hour, white cell count 4·1 × 10⁹/l and haemoglobin concentration 16·0 g/dl; serology (toxoplasma, viral antibodies) yielded negative results. Nine months later he remained well with no residual lymphadenopathy.

**LIGHT MICROSCOPY**

All the nodes showed essentially similar features. Extensive, partial, or complete loss of nodal architecture with varying degrees of necrosis had occurred; and this is the first major characteristic of the lymph node pathology. The capsule was infiltrated by a mixture of lymphoid cells, and in some cases it was breached, with the proliferation of lymphoid cells extending into surrounding tissues. These cells consisted of small round lymphocytes and immunoblast-like cells similar to those seen in the interfollicular areas of the nodes. Some follicles with germinal centres were preserved but often difficult to distinguish (Fig. 1). The necrotic foci seemed to start in the cortex and paracortex but were often large and confluent and in one case affected the entire node. The central areas of these foci (Fig. 2) consisted of a coagulative structured type of necrosis, in which palely eosinophilic staining and degenerating lymphoid cells were seen. Ghost outlines of vessels were also seen. Reticulin stains showed the vascular component well (Fig. 3).

Scattered throughout the necrotic zones were irregular pyknotic haematoxyphilic fragments of nuclear and cellular debris. These areas gradually faded into regions in which the cells were better preserved with identifiable histiocytic features but with many degenerate forms (Fig. 4). Beyond the edges of these foci, where the cells were largely viable, was a population of cells consisting of recognisable small mature lymphocytes, immunoblasts, and many histiocytic cells, with varying amounts of pale indistinct cytoplasm and vesicular, sometimes irregular or indented nuclei (Fig. 5). A Giemsa stain clearly showed the cytoplasm as a grey rim. Some of these cells seemed to be phagocytosing nuclear debris (Fig. 6). The presence of these cells (histiocytic) is the second important characteristic feature of this disease process. This mixed population of cells with a prominent histiocytic component bordering the necrotic foci showed gradually decreasing evidence of pyknosis and degeneration further away from the edge of the necrotic foci towards normal interfollicular tissue. In some areas the histiocytic cell infiltrate was almost like a sheet, but there were no granulomas. The third consistent feature in these nodes was absence of a neutrophil polymorph continuous infiltrate.

The Table summarises the pathological features.

**ELECTRON MICROSCOPY (CASE 3)**

The areas adjacent to the necrotic foci showed a mixture of cells (Fig. 7). Some were characterised by cytoplasm containing lysosomes and vacuole-associated myelin figures, presumably corresponding to

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Fig. 5 Case 1: beyond the immediate edges of necrotic focus there is a mixed population of lymphocytes, immunoblasts, plasmacytoid cells, and histiocytic cells with phagocytosed debris. (Haematoxylin and eosin.) × 400.

Fig. 6 Case 1: histiocytic cells, some of which have ingested nuclear debris. (Haematoxylin and eosin.) × 800.
the histiocytic cells seen at light microscopy; occasional plasma cells; and cells containing mitochondria and varying amounts of rough endoplasmic reticulum representing transforming lymphocytes. An occasional simple tubuloreticular structure was identified on review of the electron micrographs (Fig. 8) as reported by others.\(^{16}\) Cells with moderately abundant rough endoplasmic reticulum containing phagosomal bodies were seen, suggesting in some instances that many of the so called histiocytic cells are, in fact, cells of the lymphoid series.

One of the nodes stained for lysozyme (case 1) showed a variable degree of finely granular positivity; the positivity was variable within a given section. Staining for \(\alpha_1\)-antitrypsin (case 3) showed small numbers of positive cells, fewer than would have been expected from their histiocytic, histological appearances, supporting the idea that many of these cells are lymphocytic in origin rather than histiocytic.

**Discussion**

Necrotising lymphadenitis without granulocytic infiltration has been well documented by the Japanese,\(^{1-11}\) and recently a series from North America was described\(^{12}\) in addition to three cases from Greece and Vietnam.\(^{13}\) These are the first four cases to be described in the United Kingdom, although undoubtedly cases have been seen by those with a special interest in lymph node disease (AG Stansfeld, 1983; MH Bennett, 1983; personal communications).

The disease presents with cervical lymphadenopathy, which may be painful and tender but rarely spreads to other groups of nodes. There is often accompanying leucopenia and a low neutrophil count. The disease is entirely benign.

**Summary of histopathological findings in necrotising lymphadenitis**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Histiocytic cells around necrotic foci</th>
<th>Necrosis</th>
<th>Polymorphs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>++++</td>
<td>Scattered areas</td>
<td>Absent</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>Extensive areas</td>
<td>Absent</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>Extensive areas</td>
<td>Absent</td>
</tr>
<tr>
<td>4</td>
<td>++</td>
<td>Massive areas</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Numbers of histiocytes = (+) moderate, (++) large, (+++) massive.
The nodes are often biopsied as the lymphadenopathy may increase in size and continue for some weeks to simulate lymphoma, tuberculosis, or other lymph node disease. Histologically, the disease is characterised by coagulative necrosis, an infiltrate of histiocytic cells, varying degrees of loss of nodal architecture, and an absence of polymorphs. The main differential histological diagnoses are lymphoma, vascular infarction of a node, systemic lupus erythematosus, bacterial lymphadenitis, and pseudolymphomatous necrotising lymphadenitis.\textsuperscript{12} 14 15

The polymorphous and reactive nature of the cells around the necrotic areas excludes lymphomas of the lymphocyte series, but the distinction may be difficult, and one case was initially mistakenly thought to be lymphoma (case 2). The lack of cytologically malignant features, together with the polymorphous nature of the infiltrate away from the zones adjacent to the foci of necrosis, exclude malignant histiocytic disorders. In vascular infarction of a node a thrombosed vessel, usually associated with tumour infiltration, is found in or near the capsule. Bacterial lymphadenitis shows extensive suppuration with formation of abscesses and many polymorphs, and reactive follicles are seen in the rest of the node.

Systemic lupus erythematosus is the most difficult differential diagnosis, but the complete absence of polymorphs is a good clue. In this condition there may also be vasculitis, an onion skin formation in the thickened vessel walls, and fibrinoid necrosis within residual follicles, although these features are rare.\textsuperscript{19} Even more uncommon is the finding of haematoxyphil bodies. Pseudolymphomatous necrotising lymphadenitis is another disorder recently reported from Okinawa. It is distinct from necrotising lymphadenitis in that there is an overwhelming infiltrate of immunoblasts in the nodes, although Michalek and Henzan did not refer to its differentiation from necrotising histiocytic lymphadenitis.\textsuperscript{14} The separation of the two is important, particularly in view of the association of the disease seen in Okinawa with a rapidly fatal lymphoma. The exact nature of the proliferating and degenerating cells in necrotising lymphadenitis is uncertain. The foci occur in the parafollicular T cell areas, but originally the participating cells were regarded as histiocytes.\textsuperscript{12} An ultrastructural study suggested that at least some of the cells were of

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Case 3: histiocytic cell (HC) containing myelin figures and transforming lymphocytes (TL), containing tubuloreticular structure (TRS) (inset). (Electron microscopy $\times$ 6000.)}
\end{figure}
transformed lymphocyte or immunoblast lineage.16 The cells did not show large numbers of lysosomal bodies and the ruffled border characteristic of histiocytes. They did, however, have short runs of endoplasmic reticulum, and transitional forms between immunoblasts and typical histiocytic cells (as judged by conventional light microscopy) were seen ultrastructurally. This finding has been amply supported by a recent study using cell markers,13 in which it was shown that the necrosis in this condition developed in large foci of so called T associated plasma cells. These cells die and are then phagocytosed by histiocytes that vary in number from case to case (as found here) and from site to site within a node. T lymphoma cells may contain lysosomal granules and may undertake phagocytosis17; this would explain the presence of cells with phagosomal bodies and moderate rough endoplasmic reticulum and yet without other characteristics of histiocytes within the necrotic foci.

It is interesting to speculate that there may be a correlation between the extent of the necrosis and the extent of histiocytic cell infiltrate as the scattered necrosis in case 1 showed large numbers of these cells and smaller numbers were present with extensive necrosis in cases 2 and 3. Extensive necrosis together with an intermediate number of histiocytic cells were nevertheless seen. The extent of these two phenomena may reflect the degree of success (many histiocytes, little necrosis) or failure (few histiocytes, much necrosis) of the host in responding to the aetiologic agent causing necrosis, but other factors such as the duration of the condition probably also play a part in the resulting morphological picture.

The aetiology of the condition is unknown, although a viral aetiology is suggested by the presence of the tubuloreticular structures seen here and by Imamura et al.16 Cultured cells infected with picorna virus show myelin figures with associated vacuoles19 similar to those described here. Although there are reports of cases of this disease being associated with toxoplasma19 and yersinia,13 the serology in our cases was entirely negative as were the cultures when these were performed.

These four patients were diagnosed in Berkshire within a span of 18 months; no previous cases had been recognised in the preceding five years. The evidence is consistent with an infective aetiology.

Addendum
Since the preparation of this paper another case has been recognised (MHA) in an Iraqi woman originally diagnosed as having lymphoma.

We thank the clinicians for permission to report these cases; the electron microscopy department at the John Radcliffe Hospital, Oxford; the medical laboratory scientific officer histopathology staff and the departments of medical photography at both hospitals; and Mrs ME Roach, who typed the manuscript. Thanks are also due to Drs MH Bennett and AG Stansfeld, who confirmed the diagnoses.

References

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