Lymph node hyalinisation in rheumatoid arthritis and systemic sclerosis

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Abstract
Aims—To review the histological features of lymph nodes excised from seven patients with rheumatoid arthritis and one with systemic sclerosis.

Methods—Lymph nodes excised from seven patients with rheumatoid arthritis and one patient with systemic sclerosis over a 10 year period were examined using the stains haematoxylin and eosin, periodic acid Schiff (PAS), Masson-trichrome, and Congo red for amyloid.

Results—Of the seven nodes examined from the cases of rheumatoid arthritis, three showed definite reactive follicular hyperplasia with a prominence of plasma cells in the interfollicular areas, two showed subtotal replacement of the node by numerous sarcoïd like granulomata, and one contained a large central area of necrosis with a surrounding palisade of histiocytes. In all six cases, focal areas of PAS positive eosinophilic hyaline material were present, which did not stain with Congo red. In some cases this hyaline material was focally calcified. In the seventh patient with rheumatoid arthritis the excised lymph node was almost totally replaced by similar PAS positive hyaline material which showed extensive areas of calcification. The lymph node removed from the patient with systemic sclerosis similarly showed almost total replacement by PAS positive hyaline material.

Conclusion—In all cases the nodes contained PAS positive extracellular hyaline material to a greater or lesser degree. The lymph nodes from two of the patients with rheumatoid arthritis contained numerous sarcoïd like granulomata, further indicating a possible association between sarcoïdosis and rheumatoid arthritis. Pathologists and clinicians should include rheumatoid arthritis and systemic sclerosis in their differential diagnosis of lymph node hyalinisation of unknown aetiology.

Local or generalised lymphadenopathy may occur in up to 75% of patients with rheumatoid arthritis. Most commonly the axillary, supraclavicular, and cervical lymph nodes are enlarged, but other lymph node groups may be affected. Lymphadenopathy in systemic sclerosis has not been so well documented. In both these conditions malignant lymphoma may supervene and lymph node biopsy may be undertaken to exclude this. Previous publications on node changes in rheumatoid arthritis have commented on the extreme reactive follicular hyperplasia and prominent plasma cell infiltration of the interfollicular areas. As far as we are aware, lymph node changes have only been reported in one previous necropsy case of systemic sclerosis and the histological findings were of obliteration of the nodal architecture by extensive hyaline fibrosis.

Methods
The clinical summaries stated on the request forms of all lymph nodes submitted to the Royal Victoria Hospital, Belfast, since 1984 were reviewed. Seven patients with rheumatoid arthritis and one with systemic sclerosis were identified.

Sections from each node were routinely processed and stained with haematoxylin and eosin, periodic acid Schiff (PAS), Masson trichrome, and the Congo red stain for amyloid. The clinical notes of all eight patients were reviewed.

Results
Case Reports
Cases 1–3
Cases 1, 2, and 3 were a 50 year old man, a 59 year old woman, and a 71 year old woman, respectively. Each had had a five year, 10 year, and long history of seropositive rheumatoid arthritis, respectively. All had multiple joint disease. Case 1 developed bilateral axillary lymphadenopathy and an enlarged lymph node was removed from his right axilla. In case 2 an enlarged node was removed from the right groin, and in case 3 (a patient who developed bilateral axillary and inguinal lymphadenopathy) a node was removed from the right axilla.

Histological examination of the excised nodes in all three cases showed essentially similar features. There was a noticeable degree of reactive follicular hyperplasia with lymphoid follicles and germinal centres situated throughout the cortex and medulla of the nodes. Many of these lymphoid follicles showed a "starry-sky" appearance of tingible body macrophages in their germinal centres. In the interfollicular areas there was a mixture of small lymphoid cells, among which were
plasma cells in considerable numbers. The interfollicular areas contained focal deposits of eosinophilic hyaline material which were calcified in case 2 (fig 1). This material gave a positive reaction with the PAS stain and stained green with the Masson trichrome stain. In all three cases the material did not stain with Congo red.

**Case 4**
The patient was a 78 year old man with a long history of rheumatoid arthritis and Felty's syndrome. He had an enlarged lymph node in his right axilla. This was removed.

Histological examination showed the node to be extensively replaced by eosinophilic hyaline material which was focally calcified (fig 2). A small amount of residual lymphoid tissue was identified, particularly around the periphery of the node. This was composed mainly of small lymphocytes with occasional scattered plasma cells. No follicular structures were identified. The staining reactions of the eosinophilic hyaline material were identical with those of the above group (cases 1–3).

**Cases 5 and 6**
These comprised a 50 year old man with a 10 year history of seropositive rheumatoid arthritis, and a 67 year old woman with a long history of seropositive rheumatoid arthritis. Both had multiple joint disease. The patient in case 6 also had autoimmune hypothyroidism, pernicious anaemia, and liver cirrhosis of presumed autoimmune aetiology. In case 5 an enlarged lymph node was removed from the right side of the neck, and in case 6 an enlarged node was removed from the left axilla.

Histological examination of the excised nodes in cases 5 and 6 showed similar features. There was extensive replacement of the lymph nodes by numerous well formed sarcoid-like granulomata. These granulomata were composed of epithelioid histiocytes and Langhans' type giant cells. Small central areas of necrosis were present in a few of the granulomata. Plasma cells were identified admixed with small lymphocytes surrounding the granulomata. Between the granulomata, deposits of eosinophilic hyaline material were present, similar to those described in the previous cases (fig 3). This hyaline material was also PAS positive, stained a green colour with the Masson-trichrome stain, and was Congo red negative. The Ziehl-Neelsen stain for acid fast bacilli was negative in both cases, and fungal organisms were not identified with the PAS stain.

A chest x-ray picture of case 5 showed bilateral hilar lymphadenopathy, and following the results of the lymph node pathology, the patient underwent a Kveim test which proved positive.

After a node biopsy and before further investigation could be undertaken, case 6 died as a result of liver failure. A post mortem examination was not carried out.
of the lymph node, with a surrounding palisade of histiocytes. The remaining lymph node contained a few inactive lymphoid follicles, together with plasma cells and small lymphocytes. Deposits of eosinophilic hyaline material were also identified in interfollicular areas. This material was PAS positive, Congo red negative, and stained a green colour with the Masson-trichrome stain.

The Ziehl-Neelsen stain was negative, as was the Warthin-Starry stain for cat scratch bacilli. Fungal organisms were not identified.

Investigations performed following the biopsy included serology for toxoplasmosis, Q-fever and infectious mononucleosis. All tests yielded negative results. The lymphadenopathy disappeared and no infective cause was ever found.

Case 8
A 39 year old man with a five year history of systemic sclerosis was found to have mediastinal lymphadenopathy on chest x ray. One of these nodes was removed for histological examination.

Histological examination showed that the lymph node had been extensively replaced by eosinophilic hyaline material similar to case 4 (fig 4). Occasional inactive lymphoid follicles were present in parts of the node which were not hyalinised. In contrast to case 4, calcification was not identified in the hyalinised areas. The staining reactions of the hyalinised material were similar to those in the previous cases.

The clinical features and histological findings of the excised lymph nodes are summarised in the table.

**Summary of clinical features and lymph node histology**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age/Sex</th>
<th>Clinical findings</th>
<th>Lymph node histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/M</td>
<td>Five year history of rheumatoid arthritis. Bilateral axillary lymphadenopathy</td>
<td>Pronounced reactive follicular hyperplasia. Plasma cells in interfollicular areas. Focal deposition of PAS positive eosinophilic hyaline material</td>
</tr>
<tr>
<td>2</td>
<td>59/F</td>
<td>10 year history of rheumatoid arthritis. Enlarged node right groin</td>
<td>Pronounced reactive follicular hyperplasia. Plasma cells in interfollicular areas. Focal deposition of calcified PAS positive eosinophilic hyaline material</td>
</tr>
<tr>
<td>3</td>
<td>71/F</td>
<td>Long history of rheumatoid arthritis. Bilateral axillary and inguinal lymphadenopathy</td>
<td>Pronounced reactive follicular hyperplasia. Plasma cells in interfollicular areas. Focal deposition of PAS positive eosinophilic hyaline material</td>
</tr>
<tr>
<td>4</td>
<td>78/M</td>
<td>Long history of rheumatoid arthritis with Felty's syndrome. Enlarged node right axilla</td>
<td>Extensive replacement of node by focally calcified PAS positive eosinophilic hyaline material</td>
</tr>
<tr>
<td>5</td>
<td>50/M</td>
<td>10 year history of rheumatoid arthritis. Enlarged right cervical node</td>
<td>Numerous well formed sarcoid like granulomata. PAS positive eosinophilic hyaline material between granulomata</td>
</tr>
<tr>
<td>6</td>
<td>67/F</td>
<td>Long history of rheumatoid arthritis, autoimmune hypothyroidism, pernicious anaemia, cirrhosis. Left axillary lymphadenopathy</td>
<td>Numerous well formed sarcoid like granulomata. PAS positive eosinophilic hyaline material between granulomata</td>
</tr>
<tr>
<td>7</td>
<td>62/F</td>
<td>Four year history of rheumatoid arthritis. Enlarged nodes right axilla</td>
<td>Large central area of necrosis with surrounding palisade of histiocytes. PAS positive eosinophilic hyaline material</td>
</tr>
<tr>
<td>8</td>
<td>39/M</td>
<td>Five year history of systemic sclerosis</td>
<td>Extensive replacement of node by PAS positive eosinophilic hyaline material</td>
</tr>
</tbody>
</table>

**Discussion**

Localised or generalised lymphadenopathy may be found in up to 75% of patients with rheumatoid arthritis at some stage during the disease process. In rheumatoid arthritis lymphadenopathy is most common when the symptoms in the joint are active. The most common nodes affected are the axillary, cervical, and supraclavicular groups, although other lymph nodes may also be enlarged. Lymphadenopathy may be particularly severe in Felty’s syndrome (rheumatoid arthritis, splenomegaly, and autoimmune neutropenia) and in juvenile rheumatoid arthritis (Still’s disease). As well as lymphadenopathy, patients with rheumatoid arthritis may have associated systemic features such as fever, weight loss, and anaemia. These clinical symptoms may raise the question of a malignant lymphoma, and lymph node biopsy may be undertaken to exclude this diagnosis. The clinical suspicion may be further heightened by the increased incidence of malignant lymphoma previously reported in patients with rheumatoid arthritis.

The histological findings reported in excised nodes comprise pronounced follicular hyperplasia with large, active germinal centres. Increased numbers of plasma cells are generally found in interfollicular areas in the medullary cords.
Lymph node changes have been described rarely in patients with systemic sclerosis. As far as we are aware, only one necropsy case has been reported, and the findings were of extensive nodal replacement by hyaline fibrosis. Malignant lymphomas have also been described arising in association with systemic sclerosis and so lymph node biopsy may be undertaken to exclude this. The histological findings in cases 1, 2, and 3 were of pronounced reactive follicular hyperplasia and prominent plasma cell infiltration of interfollicular areas. These findings were similar to those reported before. In all three cases there were focal deposits of PAS positive eosinophilic hyaline material (focally calcified in case 2) in interfollicular areas. Hyaline material may be seen in burnt-out germinal centres in rheumatoid arthritis, and in other conditions where reactive follicular hyperplasia has been followed by involution of lymphoid follicles. As far as we are aware, however, the presence of such material within interfollicular areas in association with reactive follicular hyperplasia has not been commented on in other reviews of lymph node histology in patients with rheumatoid arthritis. In 1946 Poursines and Rochu mentioned lymphoid aplasia with pronounced sclerosis of the lymph nodes accompanying longstanding rheumatoid arthritis. They called this "lymph node cirrhosis". The changes they described are similar to those in case 4 in which the excised lymph node was almost totally replaced by focally calcified hyaline material. Similar hyaline material was also seen in cases 5, 6, and 7. In cases 5 and 6, numerous well formed sarcoid-like granulomata were present throughout the substance of the node. There is no doubt that in case 5 the patient also had active sarcoid disease as there was extensive bilateral hilar lymphadenopathy and the patient exhibited a positive Kveim reaction. In case 6 the patient died from hepatic failure soon after the lymph node biopsy and before it could be determined whether he had sarcoidosis. The histological findings of well formed granulomata, however, were certainly suggestive of this diagnosis.

Sarcoidosis has many features in common with various autoimmune disease. Several studies have commented on a possible association between sarcoidosis and rheumatoid arthritis. The findings in cases 5 and 6 lend further support to the existence of such an association.

In case 7, a large central area of necrosis was present in the node, with a surrounding palisade of histiocytes. The histological findings were suggestive of an infective process, but no infective cause was found despite detailed investigation following the lymph node biopsy. The findings also raised the question of a rheumatoid nodule arising in the lymph node, a phenomenon which has been described. The pattern of coagulative necrosis found in this case, however, was not typical of that found in rheumatoid nodules as the necrosis generally has a more basophilic appearance, typical of necrobiotic collagen. In the area of the node which was not affected by this necrotising process the same PAS positive eosinophilic hyaline material seen in cases 1 to 6 was also present.

In all seven cases of rheumatoid arthritis this eosinophilic hyaline material was negative with Congo red stain for amyloid. Amyloid, of course, may complicate the course of rheumatoid arthritis and has been described in lymph nodes in patients with this condition. The nature of the hyaline material in our cases was unclear. It may represent immunoglobulin which does not have a β-pleated structure when deposited in tissues, and therefore does not have the staining properties of amyloid. This material might have been produced by the plasma cells, commonly seen in nodes in rheumatoid arthritis and present to a greater or lesser degree in all of our cases examined. Interestingly, similar PAS positive amorphous eosinophilic material may also be seen in lymph nodes in angioimmunoblastic lymphadenopathy with dysproteinemias (AILD) and in nodes affected by lymphoplasmacytoid lymphomas. Again this material may represent immunoglobulin products produced by plasma cells in AILD, and by the lymphoplasmacytoid cells in lymphoplasmacytoid lymphomas. Plasma cells may, of course, be present in large numbers in AILD. Amyloid has also been reported in lymph nodes in occasional cases of AILD. Some patients with AILD have a history of an autoimmune disease such as rheumatoid arthritis, although most cases arise de novo.

We suggest that this characteristic hyaline material is produced in lymph nodes in cases of rheumatoid arthritis. Plasma cells, which are present in appreciable numbers in interfollicular areas in association with the pronounced reactive follicular hyperplasia seen in cases 1 to 3, were probably responsible. We have not seen such hyaline material in interfollicular areas of nodes showing reactive follicular hyperplasia in association with other conditions. More pronounced changes of extensive fibrosis and calcification (case 4) may occur in later stages of the disease process, in nodes where the reactive hyperplasia has subsided. These changes may lead to a confusing picture which the pathologist could find difficult to interpret.

Hyaline material, similar to that which we have described, has been referred to as paraamyloid, and it is not uncommon in advanced stages of inflammatory or neoplastic conditions affecting nodes. The hyaline material found in cases 5 and 6 may simply represent healed sarcoid granulomata, and in case 7 may represent the sequela of a healed infective process which has subsequently become reactivated. Alternatively, the material may have resulted from previous reactive changes and plasmacytosis secondary to the associated rheumatoid arthritis.

Extensive lymph node fibrosis has been reported in one previous necropsy case of systemic sclerosis. Four visceral nodes...
were examined histologically (one tracheobronchial, two bronchopulmonary, and one mesenteric) and all showed similar features. The findings described are similar to those seen in the mediastinal lymph node in case 8. The aetiology of this fibrosis is unknown, but fibrosis may be found in various other organs in systemic sclerosis.

Extensive lymph node hyalinisation is particularly common in the inguinal and iliac group of nodes. These changes may result from longstanding non-specific low grade inflammation. Hyalinisation is also common following inflammatory conditions such as sarcoidosis and tuberculosis, and in association with certain neoplastic diseases such as nodular sclerosing Hodgkin’s disease. Occasionally extensive lymph node hyalinisation may be found with no clue as to its possible aetiology. This hyaline material may calcify, in time. We suggest that rheumatoid arthritis and systemic sclerosis be added to the list of causes of lymph node hyalinisation and calcification, and that pathologists and clinicians should consider these conditions in their differential diagnosis of nodal sclerosis.