Monocytoid B cell lymphoma

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Abstract
The clinical, light microscopic, ultrastructural, immunocytochemical and cytogenetic features of a case of monocytoid B cell lymphoma were investigated. The tumour initially affected the cervical and supraclavicular nodes, but 33 months later affected the left parotid salivary gland. The patient had subclinical Sjögren's syndrome. The neoplastic cells showed characteristic morphological features and had peri- and interfibrillar distribution in the node. Immunocytochemically the tumour cells were L26, 4KB5, MB2, CD19, CD20, CD22 and IgM/X positive. Prominent plasmablastic plasmacytoid differentiation was present in the recurrent tumour, suggesting an origin from post-follicular B cells. The lymphoma cells showed unusual cytogenetic abnormalities.

Monocytoid B lymphocytes, also known as parafollicular B lymphocytes, have recently been recognised in the sinuses and paracortices of reactive lymph nodes.1-3 They were formerly described as immature sinus histiocytes because of their morphological resemblance to histiocytes,4-6 and their position in the development of B cells is unclear. Monocytoid B lymphocytes proliferate in a variety of inflammatory lymphadenopathies7 and groups of them are occasionally seen in Hodgkin's disease8 and other lymphomas.9 In 1986 Sheibani et al recorded three cases of a novel B cell lymphoma with morphological and immunophenotypic similarities to monocytoid B lymphocytes.10 Three single case reports followed11-13 and recently Sheibani's group gave an account of 21 cases of monocytoid B cell lymphoma, including their original three cases.14 Subsequently another 20 cases were studied by Ngan et al.15 We document a further example of monocytoid B cell lymphoma, as this entity is not widely recognised and in this case there was prominent plasmablastic and plasmacytoid differentiation in the recurrent tumour, a finding which may have implications for determining the ontogeny of the cell of origin. Moreover, the lymphoma cells showed an unusual karyotype.

Case report
A 33 year old Caucasian woman presented with enlarged lymph nodes in the left submandibular region (3 × 3 cm) and left supraclavicular fossa (3 × 3 cm). X ray pictures and computed tomograms did not show any other sites of disease and a bone marrow aspirate and trephine biopsy specimen were normal. A polyclonal increase in serum γ globulin (total globulin 55 g/l; normal range 21–38 g/l) was noted but there were no other biochemical abnormalities. After excision biopsy of the submandibular node the patient received three cycles each of ifosfamide/etoposide alternating with doxorubicin/cyclophosphamide and entered a complete remission. She remained well and disease free for 22 months but then developed a 3 × 2 cm node in the right mid-cervical region. Recurrent disease was confirmed histologically and treatment with a weekly schedule of chemotherapy comprising doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, and prednisolone [VAPEC-B] was started. Complete remission was again rapidly achieved and on completion of chemotherapy radiation treatment to the right neck was given (2500 cGYS over nine days).

Three months later borderline hypothyroidism was diagnosed and thyroxine 50 μg daily was given. The second remission lasted 11 months when a mass 5 × 4.5 cm developed in the left parotid and salivary gland. Superficial parotidectomy was performed and, in the absence of disease elsewhere, was followed by local radiotherapy (2500 cGYS over eight days). Two further bone marrow aspirates and trephine biopsy specimens were free of lymphoma. The patient remained well and apparently disease free three months after the second relapse.

Apart from mild thyroid dysfunction the patient did not have a personal or family history of clinical autoimmune disease. Immunological studies, however, showed subclinical Sjögren's syndrome. Serum antibodies to extractable nuclear antigens (antiRo, strongly positive and anti-La, very strongly positive) were identified, and serological tests for anti-nuclear factor and rheumatoid factor were also positive. However, assays for antimitochondrial antibodies, IgG and IgM antibodies to double strand DNA, and antibodies to salivary duct epithelium were negative.

Methods
Tissues from the two lymph node biopsy specimens and the parotidectomy specimen were fixed in 10% buffered neutral formalin. Paraffin wax sections were prepared by conventional methods and stained with haematoxylin and eosin, periodic acid Schiff with and without diastase, methyl green pyronin, Giemsa, and Gordon and Sweet's...
method for reticulin. Immunocytochemical stains were performed using the avidin-biotin complex technique. The antibodies used and their sources are listed in table 1. Fresh tissue was obtained from the parotidectomy specimen and this was used for frozen section immunocytochemical and cytogenetic studies. The antibodies used are listed in table 2. Appropriate positive and negative controls were performed for both paraffin wax and frozen section immunocytochemistry.

For cytogenetic studies, the material was collected in Hanks’s basal salt solution. The sample was immediately transported to the laboratory. A cell suspension was made by mincing the tissue in a Petri dish. The cells were cultured overnight in Hams F-10 supplemented with 20% fetal bovine serum. Colcemid (0.05 μg/ml) was added to the cultures, followed after one hour by KCl (0.075M). Cells were fixed several times in methanol:acetic acid (3:1 by volume) and slides were prepared by air drying. Slides were counterstained with 5% Giemsa. All adequate metaphase spreads were analysed, photographed, and karyotyped.

For electron microscopic examination, tissues from the second and third biopsy specimens were retrieved from formalin and processed by standard methods into Agar 100 Epontyl epoxy resin. Ultrathin sections, stained with uranyl acetate and lead citrate, were examined with an AEl 801 electron microscope.

### Table 1 Immunocytochemical results in paraffin wax section

<table>
<thead>
<tr>
<th>Antibodies (CD No)</th>
<th>Major reactivity</th>
<th>Source</th>
<th>Results in neoplastic cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCA (CD 45)</td>
<td>Most white cells</td>
<td>Dako</td>
<td>Positive</td>
</tr>
<tr>
<td>L26</td>
<td>B cells</td>
<td>Dako</td>
<td>Positive</td>
</tr>
<tr>
<td>4KB5 (CD 45R)</td>
<td>B cells</td>
<td>Dako</td>
<td>Positive</td>
</tr>
<tr>
<td>MB2</td>
<td>B cells, many epithelial and endothelial cells</td>
<td>Dako</td>
<td>Positive</td>
</tr>
<tr>
<td>MT1 (CD 43)</td>
<td>T cells, granulocytes and macrophages</td>
<td>Clonab</td>
<td>Negative</td>
</tr>
<tr>
<td>UCHL1 (CD 45RO)</td>
<td>T cells, granulocytes and macrophages</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>IgG</td>
<td>B cells</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>IgM</td>
<td>B cells</td>
<td>Dako</td>
<td>Positive—cytoplasmic perinuclear ring-like</td>
</tr>
<tr>
<td>K &amp; L-light chains*</td>
<td>Histiocytes and a variety of other cells</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>± 1 antitrypsin*</td>
<td>Histiocytes</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>± 1 antichymotrypsin*</td>
<td>Histiocytes</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>Muramidase*</td>
<td>Interdigitating cells in lymph nodes, Langerhans' cells and a variety of other cells</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>Mac 387*</td>
<td>Histiocytes</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>S100 protein</td>
<td>Histiocytes</td>
<td>Dako</td>
<td>Negative</td>
</tr>
<tr>
<td>KP1 (CD 68)</td>
<td>Hodgkin cells, Sternberg-Reed cells activated T and B cells and plasma cells</td>
<td>Dako</td>
<td>Diffuse cytoplasmic positivity in the second node</td>
</tr>
<tr>
<td>Ber-H2* (CD 30)</td>
<td></td>
<td>Dako</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*Sections treated with trypsin.

### Results

**HISTOLOGICAL ANALYSIS**

In the first lymph node biopsy specimen a few residual follicles with germinal centres and irregular islands of normal lymphoid tissue were retained, but in other respects normal architecture was replaced by diffuse lymphoma (fig 1). In places the neoplastic cells occupied distended sinuses and surrounded residual follicles. In the second biopsy specimen normal architecture had been completely replaced.

The neoplastic cells in the first biopsy specimen were monomorphic and medium sized. They contained central or slightly eccentric nuclei which were oval, indented, or slightly twisted; chromatin was coarse and evenly distributed with one to three indistinct nucleoli. The most conspicuous feature was the presence of abundant pale eosinophilic or clear cytoplasm with distinct cell membranes (fig 2A); it was slightly to moderately pyroninophilic and glycogen was not demonstrable. There was a moderate degree of mitotic activity. An admixture of mature plasma cells was present and occasional epitheloid histiocytes were seen. Dilated vascular spaces containing neoplastic cells were noted, mimicking the blood lakes of hairy cell leukaemia (fig 3).

In the second node biopsy specimen the cells were larger with blastic features and brisk mitotic activity. Most of the blast cells exhibited plasmablastic features. Many intensely pyroninophilic plasmacytoid cells were also present (fig 2B), some of which contained intranuclear inclusions similar to Dutcher bodies. Only focal aggregates of monocytoïd cells were seen.

Sections of the parotidectomy specimen showed disruption of acini with formation of numerous epimyoepithelial islands. The latter were surrounded and infiltrated by neoplastic monocytoïd cells which looked identical with
the cells in the first node biopsy specimen (fig 4). Around the neoplastic infiltrates aggregates of small lymphocytes and numerous reactive plasma cells with Russell bodies were seen.

**IMMUNOCYTOCHEMICAL STAINING**

The results in tables 1 and 2 indicated a B lineage. In paraffin wax sections the neoplastic cells in all three specimens were positive for LCA, L26 (fig 5A), 4KB5 and MB2. There was also strong perinuclear positivity for IgM. Kappa light chain restriction was shown in these cells (figs 5B and C), although the staining was relatively weak in the first and third specimens. Cells within the dilated vascular spaces also exhibited pan B-cell marker and IgM/K positivity. Stains for histiocytes (KP1, Mac387, and muramidase) yielded negative results. Immunocytochemical stains on frozen sections showed CD19, CD20, and CD22 positivity. Stains for T cells and CD25 were negative.

**ELECTRON MICROSCOPICAL EXAMINATION**

The monocytoid lymphocytes measured 12–19 μm in diameter (mean 14 μm). Nuclei were variable in shape but were often reniform (fig 6); a small amount of marginal hetero-
chromatin was present and in some cells up to three nucleoli were seen. Nuclear pockets were not identified. Cytoplasmic organelles varied in number and some cells contained abundant polyribosomes with few other organelles. Some contained a small paranuclear collection of lysosomes. Neither ribosome-lamella complexes nor immunoglobulin aggregates were seen.

Some cells showed varying degrees of plasmacytic differentiation represented by variable numbers of rough endoplasmic reticulum cisternae (fig 7). Occasionally a cell contained Russell bodies.

**CYTOGENETICS**
A complex karyotype was observed in all cells examined, with variation from cell to cell.
The most frequently observed chromosomal changes included del [X] [q26], 2p+, 5q+, +6q+, +18.

Discussion
This case of monocytoid B cell lymphoma is typical in its clinical presentation, morphological features, and immunophenotype, but unusual in showing prominent plasmacytoid differentiation in the recurrent tumour. Involvement of salivary gland and association with Sjögren’s syndrome have been documented previously. In our patient with subclinical Sjögren’s syndrome the disease initially presented in the lymph nodes but subsequently affected the parotid gland. The main histological differential diagnoses are of T cell lymphoma and hairy cell leukaemia. T cell lymphoma may be suggested by the para-cortical distribution and cytomorphology of the neoplastic cells but immunophenotyping easily precludes this diagnosis. Hairy cell leukaemia rarely affects lymph nodes and is usually confined to spleen and bone marrow; monocytoid B cell lymphoma, on the other hand, is mainly a nodal disease, only occasional cases showing bone marrow and peripheral blood disease. This aside, the cytology and distribution of hairy cell leukaemia, when it does affect nodes, closely resembles monocytoid B cell lymphoma, and in our case there were even vascular spaces containing neoplastic cells, as in hairy cell leukemia, a feature which has not been described in the previously reported cases. Phenotypically, both tumours are of B lineage but in monocytoid B cell lymphoma the cells lack tartrate-resistant acid phosphatase activity, IL2 receptor, and, ultrastructurally, ribosome-lamella complexes.

The ontogeny of monocytoid B cell lymphoma is in doubt and a relation with hairy cell leukaemia has been suggested. Our case showed plasmablastic and prominent plasmacytoid differentiation confirmed histologically, ultrastructurally, and by staining with Ber-H2, the latter being a feature of normal and neoplastic plasma cells. Plasmacytoid differentiation was also reported in two previously documented cases of monocytoid B cell lymphoma. Cousar et al suggested that monocytoid B cell lymphomas originate from post-follicular B cells; our findings support this suggestion.

Morphological and immunophenotypic similarities exist between monocytoid B lymphocytes, splenic marginal zone lymphocytes,
and the centrocye-like cells of mucosa associated lymphoid tissue (MALT), and Isaacsan has pointed out that there is "considerable overlap" between MALT lymphomas and monocytoid B cell lymphomas, about 20% of the latter presenting in mucosal sites. In our case it might be argued that the occurrence of the parotid gland lesion supports this view and that the tumour is actually a MALT lymphoma with nodal disease. The fact that the patient presented with nodal disease 33 months before the salivary gland lesion was detected, however, is difficult to explain on this basis.

Evidence from the two substantial series so far published indicates that monocytoid B cell lymphoma is a low grade lymphoma. Ngan et al have shown that less than 10% of the cells in monocytoid B cell lymphoma exhibited reactivity with the proliferation antigen Ki-67, which is compatible with its indolent behaviour. Like other low grade lymphomas progression of monocytoid B cell lymphoma to a high grade lymphoma is known to occur in a small number of cases. Our patient was alive and well 36 months after presentation despite two recurrences and transformation to a high grade morphology.

The cytogenetic features of monocytoid B cell lymphoma have not been reported previously. The abnormalities of chromosomes 6 and 18 have previously been reported in non-Hodgkin's lymphomas but our case showed unique karyotypic features, the clinical importance of which is as yet unknown.

Addendum

Since the submission of this paper another paper on monocytoid B cell lymphoma has been published by Cogliatti et al. These authors described the clinical, pathological, and prognostic features of 21 cases of this neoplasm. Three of their cases exhibited plasmacytoid differentiation and in one the salivary gland was affected but the patient had no evidence of Sjögren's syndrome. The prognosis of their cases was similar to that of other low grade non-Hodgkin's lymphomas.

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