Childhood B cell lymphomas arising in the mediastinum

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Abstract

Aims—To report the clinical features and pathology of four childhood cases of primary mediastinal non-Hodgkin's lymphoma of non-lymphoblastic pathology.

Methods—Biopsy material was fixed in formol-saline and routinely processed and stained. Immunohistochemical staining was performed on paraffin wax embedded sections using the alkaline phosphatase anti-alkaline phosphatase method.

Results—The four patients presented with a large mediastinal mass and symptoms consistent with superior vena cava syndrome secondary to lymphoma. None of the patients had any clinically important disease outside the mediastinum. The four tumours had a histological appearance similar to diffuse large cell non-Hodgkin's lymphoma with sclerosis. Immunohistochemical staining showed that these tumours were of B cell origin. One patient died from infection during treatment and two patients died with progressive disease. The remaining patient remained well 43 months off all treatment.

Conclusions—These four cases further illustrate the heterogeneity of paediatric large cell lymphomas. Clinically, they seem to be equivalent to the B cell lymphoma of the mediastinum, sclerosing type, that is seen in young (predominantly female) adults. The clinical and biological features of this type of tumour in childhood are largely unknown. Using standard treatment protocols, this tumour seems to have a poor prognosis and its optimal treatment therefore requires further clarification.

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Children with Hodgkin's disease (usually of nodular sclerosing type) or T cell lymphoblastic lymphoma often present with symptoms caused by a large mediastinal mass. Over the past decade it has become apparent that in adults the mediastinum can also be the primary site for non-Hodgkin's lymphomas (NHL) of non-lymphoblastic morphology. These lymphomas have been allocated to a variety of histological subtypes, making it uncertain whether they constitute a single clinical entity.¹⁻¹⁰ The sclerosing, diffuse large cell lymphomas of the mediastinum do, however, seem to have a characteristic

presentation, clinical course, and histology.^{8,9} This malignancy, which predominantly affects young adult women, is characterised by its extremely rapid growth, large bulk, and early extranodal extension in the absence of generalised lymphadenopathy. Sclerosis is the most prominent microscopic feature of these tumours.^{3,7} Recent reports have suggested that these tumours are of B cell origin and may arise in the thymus.^{9,10}

Methods

Four children with diffuse large cell lymphoma with sclerosis arising in the mediastinum were identified. Three of the cases were identified at presentation and the remaining case (case 1, table 1) was identified as part of an ongoing retrospective study of paediatric non-Hodgkin's lymphoma. Among the four children were three boys aged 2, 6, and 11 years at diagnosis, and one girl aged 11 years.

In each case biopsy tissue, fixed in formol-saline, was routinely processed and stained. Sections were also stained with a panel of antibodies known to work in routinely processed tissue (table 2). These included monoclonal antibodies to the leucocyte common antigens CD45 (LC1), CD45R (4KB5), and CD45RO (UCHL1), a pan-B cell antibody CD20 (L26), the β chain of the T cell receptor, CD30 (Ki-1 antigen), and MAC 387. Sections were also stained with a polyclonal antibody to the CD3 antigen.¹¹

Sections were also stained for the expression of desmin, neuron specific enolase, S-100, cytokeratin and epithelial membrane antigens.

Results

The salient clinical features of the four patients are summarised in table 1. Briefly, all four patients had a large mediastinal mass and symptoms consistent with superior vena cava syndrome secondary to lymphoma. None of the patients had any clinically important lymphadenopathy or hepatomegaly. Haematological and biochemical investigations, including an examination of bone marrow and cerebrospinal fluid showed no abnormalities to indicate a diagnosis.

Case 1 received treatment according to Medical Research Council UKALL X protocol, schedule D,¹² with additional irradiation to the mediastinum of 1500 cGy. This entailed a four drug induction regimen

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Table 1 Clinical details at diagnosis and response to treatment

Case No	Sex	Age	Presentation	Treatment outcome
1	M	6y	Cough, dyspnoea SVC obstruction	Poor clinical response, tumour progression at 7 m; died 11 m
2	F	11y	Chest and L shoulder pain L pleural effusion pericardial effusion Stridor, weight loss	Complete remission, 43 m off all treatment
3	M	2y		Poor clinical response, died 5 m into treatment of bronchopneumonia
4	M	11y	Chest pain, cough, dyspnoea, pleural effusion	Complete remission, relapsed at 6 m in mediastinum; died 10 m after diagnosis

SVC = Superior vena cava.

(daunorubicin, vincristine, prednisolone and L-asparaginase), craniospinal prophylaxis with intrathecal metotrexate and cranial irradiation (1200 cGy), and 2 modules of intensification (daunorubicin, cytarabine, etoposide and 6-thioguanine). Review following this second module of intensification treatment showed only a partial reduction in size of his original tumour. After the appearance of a soft tissue mass in the right temporalis muscle, confirmed on biopsy to be lymphoma, his treatment was changed to the CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone) regimen. There was some improvement in his condition but this proved transitory. His disease progressed and he developed a facial nerve palsy which a computed tomogram showed was due to an intracranial deposit. Subsequently, he gradually deteriorated and died.

Case 2 received three cycles of the UKCCSG B cell lymphoma protocol (MACHO).¹³ This entailed repeated courses of cyclophosphamide, vincristine, and adriamycin with high dose methotrexate and high dose cytarabine. This was followed by irradiation to residual tumour in the mediastinum (total tumour dose 3000 cGy). A computed tomogram 12 months after completion of treatment still showed some residual tissue surrounding the heart and great vessels; this appeared calcified and was probably scar tissue. At the time of writing the patient had survived 50 months from diagnosis and 43 months off all treatment.

Case 3 was treated with the UKCCSG B cell lymphoma protocol (MACHO), as for case 2. Unfortunately, he showed only a limited response to treatment. He died of bronchopneumonia while extremely neutropenic.

Case 4 began chemotherapy with UKCCSG NHL protocol 1 (8501). This entailed two courses of CHOP alternating

with methotrexate and etoposide. There was a rapid and complete clinical response. Further treatment involved intensification with cytarabine, thioguanine, and asparaginase. Subsequent maintenance treatment comprised alternating courses of CHOP, cytarabine and thioguanine, methotrexate and etoposide.

Six months after diagnosis, when he was due to complete chemotherapy, he again developed superior vena cava obstruction. A computed tomogram showed recurrent disease in the anterior mediastinum, peripheral lung lesions, a 6 × 8 cm para-aortic node mass and deposits in both kidneys. Bone marrow and cerebrospinal fluid were once again clear. He received mediastinal irradiation with radiological resolution of his mediastinal mass. This was followed by reinduction chemotherapy according to the Medical Research Council UKALL X protocol. He also received an early module of intensification treatment. Despite this he developed progressive disease in para-aortic nodes, liver, and kidneys with substantial renal impairment. At this time he received irradiation to both kidneys with biochemical improvement in his renal function. He developed grand mal seizures and a computed tomogram showed multiple enhancing intracerebral lesions. Active treatment was discontinued and he died 10 months after diagnosis.

HISTOLOGICAL APPEARANCES

Diagnostic tissue was obtained by thoracotomy in all four cases. The histology of the four cases was very similar, showing a diffuse non-Hodgkin's lymphoma with morphological features of follicular centre cells. A degree of sclerosis was present in every case, with the tumour cells being compartmentalised by narrow irregular collagen bundles (fig 1). The cells were predominantly large, the nuclei showing considerable variation in size and shape, either non-cleaved (centroblasts) or large cleaved cells (centrocytes) (fig 2) as well as occasional cells with large rounded nuclei and a single central nucleolus (immunoblasts). In two of the tumours (cases 3 and 4) the sclerosis was more extensive and this was associated with a stromal infiltrate of lymphocytes; areas of necrosis were present in one case (case 4).

A postmortem examination was carried out on case 3. This showed a residual upper mediastinal mass measuring 10 × 6 × 2 cm, which incorporated the thymus and extended around the apex of the left upper lobe of the lung, around the hilar vessels and around the arch of the aorta (fig 3). Several coronal slices of the dissected mediastinal mass were examined; these showed extensive fibrosis and necrosis but no tumour. Several lymph nodes were examined, but again no evidence of tumour was found. Examination of the lungs showed bilateral bronchopneumonia.

All four cases had a similar staining pattern with the antibodies used (table 2). That these cases were indeed lymphomas was confirmed by their positive staining reaction with the

Table 2 Immunohistochemistry results

Antibody	Case 1	Case 2	Case 3	Case 4
CD45 (LC-1)	+	+	+	+
CD20 (L26)	+	+	+	+
CD45R (4KB5)	+	+	+	+
CD45RO (UCHL1)	-	-	-	-
CD3	-	-	-	-
T8F1	-	-	-	-
EMA	ND	-	+	ND
BER-H2	-	-	-	-
MAC-387	-	-	-	-
Cytokeratin	-	-	-	-

ND = not determined.

Figure 1 Sclerosis with fine collagen bands surrounding small and large groups of tumour cells (haematoxylin and eosin.)

Figure 2 Higher magnification showing centrocytic centroblastic cells (haematoxylin and eosin.)

antibody to the CD45 antigen (leucocyte common antigen). The tumour cells were negative for cytokeratin, desmin, neuronal specific enolase and S-100. A B cell origin for these tumours was confirmed by their expression of the CD20 (fig 4) and CD45R0 (UCHL1) and lack of expression of the CD45RO (UCHL1) and CD3 antigens. The tumour cells were also negative on staining for the β chain of the T cell receptor. All four cases were negative for the Ki-1 antigen (CD30).

Discussion

In the paediatric oncology clinic malignant lymphomas of the anterior mediastinum are predominantly of two types—namely, either T cell lymphoblastic lymphomas¹⁴ or nodular sclerosing Hodgkin's disease.¹⁵ The cells of T cell lymphoblastic lymphoma contain nuclear TdT and lineage restricted markers that correlate with T cell intrathymic differentiation.¹⁶ The nature of the neoplastic cells in Hodgkin's disease remains a subject of considerable controversy,^{17,18} nevertheless, it is known that Hodgkin's disease shows a tendency to affect T cell areas in lymph nodes and spleen, such that the origin of primary disease in thymic tissue is not without precedent. Several published reports have drawn

attention to lymphomas of the anterior mediastinum in young adults that do not belong to either of the above categories and over 100 such cases have now been described.¹⁻¹⁰

Clinically, these large cell tumours arise in the anterior mediastinum, infiltrate extensively within the thorax, and only infrequently spread to involve extrathoracic viscera. The lymphomas presented here followed a similar clinical course. In contrast to the T cell lymphoblastic lymphomas, which predominantly affect adolescent males, these large cell lymphomas have been reported as occurring predominantly in young adult women. Sclerosis, often of the fine compartmentalising type, has been described as a common microscopic feature of these tumours and is evident in the cases described here. Sclerosis in non-Hodgkin's lymphomas has been described as a microscopic feature by several authors,¹⁹⁻²¹ it is not, however, a feature in the prevalent forms of paediatric lymphoma.

Some authors have classified these tumours as immunoblastic sarcoma of either B or T cell type, or follicle centre cell lymphoma of large cleaved type or non-cleaved type.^{2,4,5,22} Classification by morphology alone is clearly unsatisfactory, particularly the assignment of presumptive cell type, and may have led to a false impression of the heterogeneity in this group of lymphomas. Two of the more recent reports^{9,10} have established the B cell origin of these tumours, and the immunohistological staining results reported here support these findings. The demonstration of surface

Figure 3 Large mediastinal mass removed at post mortem examination from case 3³; the mass involved the thymus and surrounding tissues (arrowed). Histological examination showed extensive fibrosis with small islands of thymic tissue, but no residual tumour.

Figure 4 Immunolabelling of the CD20 (L26) antigen, showing strong cytoplasmic staining (alkaline phosphatase-anti alkaline phosphatase technique).

immunoglobulin in routinely fixed and processed tissue is unsatisfactory, and unfixed tissue is essential for the full characterisation of immunoglobulin expression in B cell lymphomas. Although this was not possible for the cases described here, the expression of the CD45R (4KB5) and CD20 (L26) antigens clearly show a B cell origin. This experience varies from that of Bunin and her colleagues,²² who reported that of 25 children (predominantly adolescent females) with mediastinal non-lymphoblastic lymphoma, 12 cases had morphological features described as typical of peripheral T cell lymphomas. As correlative immunological studies were only presented for one case and two further cases expressed markers of B cell lineage, however, the correct immunophenotype of these cases must be regarded as unproved.

Survival data presented by Jacobson *et al*⁸ and Bunin *et al*²² suggest strongly that large cell tumours of the mediastinum are potentially curable in 50% of adults and 75% of children if treated on protocols incorporating cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP). The optimism of these two reports is, however, not shared by others.^{2,4,6,9,10} Of the four cases presented here, only case 2, who was treated according to the MACHO protocol, has completed her treatment successfully. She was alive and well without evidence of disease 50 months after diagnosis. Two cases developed extensive disease after the failure of their initial treatment. The ultimate involvement of the central nervous system in both cases and widespread abdominal disease in one case illustrates the aggressive tendency for this tumour to metastasise outside the thorax. The distribution of progressive disease is somewhat unusual for malignant lymphoma in that at no time was there evidence of peripheral lymph nodes or bone marrow disease. At present, the prognosis for children who develop this unusual lymphoma must be regarded as poor.

Addis and Isaacson¹⁰ have posed the question of whether these tumours are of thymic or nodal origin. The site of origin, lack of nodal disease, and in one case the presence of residual thymic tissue around the tumour, and the demonstration of a population of B cells with a unique phenotype in normal thymus²³ are arguments that suggest that at least some of these tumours may in fact be of thymic origin. It is, however, extremely difficult to discriminate between hilar nodal disease and thymic disease on x-ray picture, ultrasound scan, or computed tomogram. It was not possible to determine the precise anatomical origin in three cases. An interesting feature of the fourth case was the lack of involvement of a lymph node included within the mass, which suggests that this case, at least, may have been of thymic rather than nodal origin. Although the proposal of Addis

and Isaacson that these tumours arise from thymic B cells is attractive, the site of origin of these tumours must be regarded as unconfirmed until further cases are described.

In conclusion, these four cases further illustrate the heterogeneity of paediatric large cell lymphomas. Clinically, they can be considered as equivalent to the B cell lymphoma of the mediastinum, sclerosing type, that is seen in young adults. The incidence of this type of lymphoma in childhood and its optimal treatment require further clarification.

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