Pergamon

Oral Oncol, Eur J Cancer, Vol. 30B, No. 3, pp. 155–159, 1994

0964–1955/94 $7.00+0.00

Lymphomas of the Head and Neck 2; the B-cell Lymphomas

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INTRODUCTION

LYMPHOMA PRESENTING in the head and neck can be divided into the nodal and extra-nodal groups. It is the latter that cause the most difficulty for the clinician. Approximately 25% of extranodal lymphoma occurs in the head and neck [1–3] and includes four notable variants of non-Hodgkin lymphoma; nasofacial T-cell lymphoma, salivary gland lymphoma, Burkitt's lymphoma (BL) and Waldeyer's ring lymphoma. Although Reed–Sternberg-like cells may be seen in these lymphomas, true Hodgkin's disease is rare in these sites.

Nasofacial T-cell lymphoma was the subject of a previous review [4], this article will deal with the tumours derived from the B-cell system. Extranodal lymphoma can occur anywhere in the head and neck but since the largest concentration of lymphoid tissue is in Waldeyer's ring, this is the site of lymphoma in 66% of cases [2].

CLINICAL FINDINGS

The clinical features at presentation vary according to the site of the lymphoma but in most cases symptoms can be related to the presence of a mass [5]. Most patients with tonsillar lymphoma present with a history of sore throat or lump in the throat, those with nasopharyngeal lymphoma with the symptoms of nasal obstruction or decreased hearing, while lymphomas at the base of the tongue lead to sore throat or dysphasia. Systemic symptoms are unusual [5–16]. Occassionally lymphoma may involve a tooth socket but it is unlikely to be the sole site of disease [12].

DIAGNOSIS

Many authors report on the difficulty of arriving at a correct diagnosis on conventional haematoxylin and eosin staining [6, 10]. Most laboratories now use markers to leucocyte common antigen (CD45) and cytokeratin to differentiate between lymphoma and carcinoma. Other markers to CD20 (B-cells), CD3 and CD45RO (T-cells), and S100 (neural tissue and melanocytes) are needed to confirm the type of lymphoma and exclude other tumours such as malignant melanoma [10]. Reactive inflammatory processes have also to be excluded but these can usually be distinguished on morphological or clinical grounds. Epstein–Barr virus infection of the tonsil can give the most bizarre appearances and trap even the most wary of pathologists [13]. Close cooperation between pathologist and clinician is essential to maximise the diagnostic yield from small biopsy specimens [10].

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Recieved 20 May 1993; accepted 26 May 1993.

WALDEYER'S RING LYMPHOMA

Waldeyer's ring is a circular band of lymphoid tissue at the opening of the aerodigestive tract and includes the tonsils and the lymphoid tissue of the nasopharynx and base of tongue.

It is the primary site of involvement in 5% of patients with non-Hodgkin's lymphoma [2]. Saul and Kapadia [14] reported 68 patients with primary lymphoma of Waldeyer's ring, 51% involved the tonsil, 35% the nasopharynx, 9% the base of tongue while 4% involved multiple areas. The mean age was 58 and the male to female ratio 1.1 to 1. 89% of patients were stage I or II at presentation, most having intermediate grade histology, with cleaved cells (centrocytes) predominating. 8 out of 10 patients with extra nodal disease developed problems in the gastrointestinal (GI) tract, emphasising the relationship between the Waldeyer's ring and the gut [15]. Weiss *et al.* demonstrated the presence of Epstein–Barr virus in 2 of 10 patients with Waldeyer's ring lymphoma [16].

SALIVARY GLAND LYMPHOMA

Primary malignant lymphoma accounts for 2.5% of primary salivary gland tumours and 5% of all primary extra nodal malignant lymphomas [1, 2, 17].

Most patients present in their fifth or sixth decade with a lump, 70–90% involving the parotid gland. The predominance within this gland is due to the presence of lymph nodes which can be found in up to 80% of normal patients [18].

Salivary gland lymphoma should, therefore, be regarded as two separate diseases; involvement of lymph nodes embedded within the salivary gland and involvement of the salivary tissue proper [19]. It is important to separate the two diseases since their clinical features and course are different. Nodal tumours in the salivary gland behave like other nodal lymphomas elsewhere and tend to spread to involve other lymph node groups, the spleen and bone marrow. True salivary gland lymphoma frequently arises on the background of autoimmune disease such as Sjogren's syndrome and is therefore more common in women. It also forms part of the mucosa-associated (MALT) lymphoma group and, therefore, may remain localised for long periods before involving other mucosal sites [19–22].

Histologically, the two lymphomas differ. Most nodal lymphomas are derived from the centroblasts and centrocytes

of the germinal centre but MALT lymphoma is derived from a specialised group of mucosal lymphocytes and always includes a significant plasma cell component [17, 19–21].

Sjogren's syndrome is associated with an increase of incidence of lymphoma by 43-fold [23]. All the reports are of B-cell lymphomas, usually lymphoplasmacytic, in which light chain restriction can be demonstrated [24–32]. Some cases have high grade histology but the occasional reports of Hodgkin's disease must be viewed with caution since Reed–Sternberg-like cells can be found in lymphoplasmacytic lymphoma [33, 34].

Sjogren's syndrome is characterised by myoepithelial sialadanitis (MESA), otherwise known as benign lymphoepithelial lesion or Mikulicz disease [35, 36]. This is a combination of lymphoid aggregates with an infiltrate of centrocyte-like cells (ccl) into a proliferative ductular epithelium. This may occur without the clinical picture of Sjogren's syndrome. MESA and lymphoma are the two ends of a spectrum of lymphoid infiltration; the evolution from one into the other is not abrupt but follows a well described pattern [20, 29].

Early MESA

The structure of the gland is preseved. Large lymphoid follicles are found adjacent to the ducts with centrocyte-like cells occupying both the marginal zone around the follicle and the hyperplastic duct epithelium. There is no evidence of clonal restriction.

Established MESA

The architecture of the gland is effaced by a florid infiltrate of lymphoid cells with germinal centres, expanded marginal zones and hyperplastic epithelial cells forming "epimyoepithelial islands".

MESA with evidence of lymphoma

In addition to the changes described above, the ccl component stands out as a clear zone around the epithelial islands while these cells and surrounding plasma cells can be demonstated to be monoclonal by immunohistochemistry.

Frank lymphoma

In some cases an infiltrate of large immunoblasts will be found accompanying the ccl and plasma cells. It is likely that all three cell types belong to the same clone but with a varying degree of differentiation.

In the early stages, the incidence of simultaneous generalised lymphoma is nil; later lesions remain confined to the salivary epithelium but as the disease progresses lymphoma may appear in cervical nodes or other mucosal sites particularly in the head and neck. A variant of mucosa-associated lymphoma known as monocytoid B-cell lymphoma is frequently found in the lymph nodes draining affected salivary glands [25, 28, 37].

Molecular biology has contributed some understanding to the field of salivary gland lymphoma. Fischleider *et al.* [38] reported uniform detection of immunoglobulin gene rearrangements in benign lymphoepithelial lesions and substantiated the presence of small monoclonal populations of cells even in the early stages. Unfortunately, in their study they did not provide histological detail as to what stage of MESA was being examined. The suggestion was made that the clonal expansion of B-cells alone is at most a prelymphomatous condition and not evidence of lymphoma.

In 1991 Falzon and Isaacson [26] reported 2 cases in which immunoglobulin light chain restriction had been shown 9 and 10 years before the development of extra-salivary gland lymphoma. They argued that monoclonality was an indication of malignancy and that the optimum management of a patient in whom a diagnosis of benign lymphoid epithelial lesion of the salivary gland is made depends on whether there is monoclonality or not. Gene rearrangement studies may be important in making this distinction but so far only Southern blotting has been evaluated. The contribution of the polymerase chain reaction, which can detect small clones of cells even in paraffin-processed tissue, awaits examination. For monoclonal lesions appropriate staging should probably be followed by an attempt at local eradication of the disease, which may be best achieved by radiotherapy. Given the tendency of MALT lymphomas to remain localised it is conceivable that this approach might prevent the progression to systemic lymphoma.

Molecular biology may help to make the distinction between nodal and extranodal lymphoma. Translocation of the oncogene *bcl* from chromosome 18 to the region of the immunoglobulin gene on chromosome 14 is characteristic of centroblastic–centrocytic lymphoma, the most common nodal lymphoma. The presence of this translocation would be evidence against a mucosa-associated lymphoma but studies involving the head and neck are rare [39, 40].

BURKITT'S LYMPHOMA

One of the most memorable pictures in medicine is that of BL involving the jaw of an African child (Fig. 1). Since the description of this tumour in 1958, BL has become one of the most studied tumours in the world. Because of the unique combination of viral indication, chromosomal translocation, interaction with the host immune system and ease of culture in the laboratory, it has been used to investigate many facets of neoplasia [41–43].

HISTORY

In 1901 Dr Albert Cook, in his paper on diseases in Africa [44], commented that the most frequent malignancy was a "sarcoma of the jaws, both upper and lower". He included a photograph taken by the Rev R.H. Levy of a patient suffering from what we now recognise as BL. In 1958, Burkitt recognised that the tumours involving the jaw and the abdominal viscera were of a similar type and suggested that these were part of the multicentric sarcoma now referred to as Burkitt's lymphoma (BL) [45]. The distribution of the disease in a band across tropical Africa suggested some environmental agent was involved in the pathogenesis. In 1960 O'Connor and Davies noted that 50% of the childhood tumours in the Kampala Cancer Registry were lymphomas with the characteristic histology of BL [46]. In 29 of the 60 cases there was jaw involvement. The geographical distribution of the jaw sarcomas was associated with the climatic requirements of the mosquito and the suggestion was made that the tumour may be caused by an arthropod-transmitted virus [47]. In February 1964, Epstein, Achong and Barr working with cultured lymphoma cells from an East Africa tumour, identified the

herpes virus now recognised as Epstein–Barr virus (EBV) [48]. Wright, in 1964, identified the origin of the lymphoma to be the marrow of the jaw, but with increased growth lymphoma cells were noted involving tooth socket gingiva and surrounding soft tissue [49]. Secondary ulceration and infection complicates the picture. In 1966, Adatia suggested that the location to the jaw was related to the developing tooth germ and there has been speculation that there may be growth factors derived from this developing epithelium that contribute to the growth of the tumour cells [50].

In 1985 Rooney *et al.* showed that EBV positive Burkitt's lymphoma cells were resistant to effector T-cells active against EBV induced cell lines [51]. The tumour cells apparently modulate their gene expression which prevents detection by the immune system [52].

The exact roles and sequence of EBV infection, mosquito bite and chronic malaria infection is a subject of much debate, which 30 years later is not resolved.

INCIDENCE

The incidence of BL in endemic areas is approximately 150 per million children [53]. BL also occurs in western populations, though it is much rarer and is referred to as sporadic BL. The incidence of sporadic BL is of the order of 1 per million [54].

CLINICAL FEATURES

The involvement of the head and neck is a characteristic feature of endemic BL occurring in approximately 60% of affected individuals; jaw involvement is much less common in sporadic BL [55]. The clinical course of BL in the untreated is progressive growth and dissemination, followed by death, frequently with CNS involvement. Modern treatment schedules now result in cure in a significant number of patients [56].

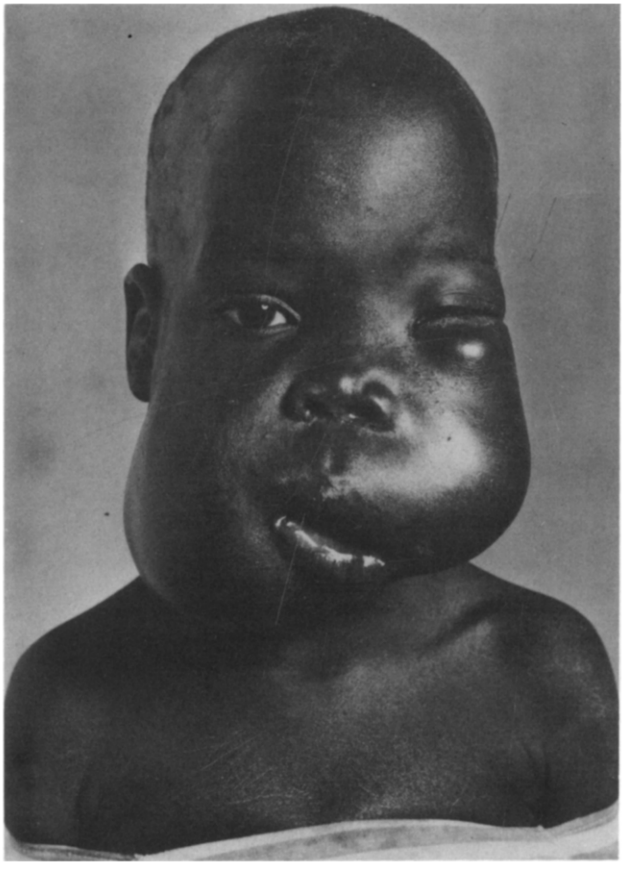

Fig. 1. African Burkitt's lymphoma involving the maxilla and mandible. (Courtesy of Dr D. Burkitt.)

PATHOLOGY

Burkitt's lymphoma is defined histologically by the appearance of medium sized round cells, some 2–4 times the diameter of a red cell [49]. On giemsa stains, there is usually a narrow rim of the blue-staining cytoplasm, which in imprint preparations contains a few lipid vacuoles. In tissue sections the cells of Burkitt's lymphoma are characteristically cohesive and have numerous macrophages containing nuclear debris, giving the sections the so-called starry sky appearance. The mitotic rate of Burkitt's tumours is very high.

Immunological techniques have defined the cells of Burkitt's lymphoma as being part of the B-cell series, expressing CD19, 20 and 22 and usually surface IgM [57–59].

The characteristic translocation of the c-*myc* oncogene from chromosome 8 to the active region of the immunoglobulin heavy chain on chromosome 14 (t8:14) was demonstrated by Dalla-Favera *et al.* and Taub *et al.* in 1982 [60–62]. Other translocations do occur but they all involve the c-*myc* oncogene and it is possible that this is responsible for the morphology and behaviour of the tumour [43].

TREATMENT AND COURSE HEAD AND NECK LYMPHOMA

Treatment of primary extra nodal lymphoma with radiotherapy alone is associated with a significant recurrence rate particularly where there is locally advanced disease or high grade histology [10]. Jacobs *et al.* [5] reported a 5-year survival for stage I and II head and neck lymphoma of between 25 and 52%, depending on the extent of radiation field used. There was a high relapse rate of central nervous system (CNS) disease in patients who had lymphoma of the paranasal sinus. It was anticipated by these and other authors that a combination of chemotherapy and local radiotherapy would improve the outcome [5, 10].

IMMUNODEFICIENCY

With the increasing use of immunosuppressive agents for transplants and the immunodeficiency resulting from HIV infection, EBV induced tumours are becoming more frequent. In these patients, immunodeficiency allows EBV to drive B-cell proliferation unopposed by cytotoxic T-cells [63]. This leads to multiple clones of B-cells proliferating and eventual transformation to high grade lymphoma. Many of these lymphomas arise in extra-nodal sites in the head and neck [64–66].

Patients with HIV infection may also develop lymphadenopathy as a result of follicular hyperplasia or monocytoid B-cell infiltration. The intra-parotid nodes may be involved in this process and these changes must be differentiated from the development of lymphoma [67].

SUMMARY

Primary lymphoma of the head and neck can be a confusing subject if the diseases are forced into the classifications and

concepts derived from nodal disease. Once it is realised that the morphology and pathogenesis of the extranodal group are related more to the mucosa associated lymphoid tissue, the behaviour of these tumours is more easily understood. EBV plays a significant role in many of the diseases including Burkitt's lymphoma and nasofacial T-cell lymphoma.

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Acknowledgements—Our thanks to Tracey Pennington for typing the manuscript and to Dr Dennis Burkitt for allowing us to use his photograph of the Burkitt's lymphoma case.