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Reviews

Lymphomas of the Head and Neck 1: Nasofacial T-cell Lymphoma

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Nasofacial T-cell lymphoma includes diseases otherwise called "lethal midline granuloma" and "necrosis with atypical cells". It is characterised by relentless destruction of nose and palate in particular but the lymphoma remains localised to the head and neck. The age of onset ranges from 10 to 87 and the survival ranges from a few months to several years. The histological appearances are of a polymorphic infiltrate but including atypical T cells in a background of macrophages. There is a strong association with Epstein–Barr virus infection.
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INTRODUCTION

THE HEAD and neck is one of the most common sites for presentation of lymphoreticular disease. Frequently this involves the cervical lymph nodes, but extra nodal presentation in the head and neck is not uncommon [1].

The sites primarily involved are Waldeyer's ring (the tonsil, nasopharynx and base of tongue), paranasal sinuses, salivary glands and oral cavity. The pathology of lymphoreticular disease affecting the nodes in the head and neck is similar to that elsewhere in the body, save for a few diseases that present more commonly in the neck, e.g. sinus histiocytosis with massive lymphadenopathy: the nodal lesions will not be discussed further. The extra nodal diseases include three well recognised, and sometimes confusing entities, nasofacial T-cell lymphoma, Burkitt's lymphoma and salivary gland lymphoma. Nasofacial T-cell lymphoma includes diseases previously called "Stewart's lethal midline granuloma", "necrosis with atypical cellular exudate", "midline malignant reticulosis" to name but a few. This subject will be reviewed in this article, a follow-up article will cover the B-cell neoplasms.

HISTORY

In 1933 Stewart [2] reported 10 cases of a condition characterised by relentlessly progressive ulceration of the nose and adjacent deep midfacial structures. Although the pathology of the cases he reported was not uniform, he considered that the condition was "granulomatous". In 2 cases the histology was said to resemble "very atypical spheroidal carcinoma", and 1 of these patients developed lung metastases; 2 other cases were classed as "sarcoma" and "Hodgkin's lymphadenoma". Despite the heterogeneous pathology Stewart felt that the cases constituted a single entity and it is from his description that the condition variously called "lethal midline granuloma", "non-healing granuloma", "granuloma gangrescens" or "midline malignant reticulosis" arose.

Friedmann [3] was impressed with the similarity of Stewart's condition to Wegener's granulomatosis (described by Wegener in 1939), and divided "non-healing granuloma" of the nose into two types—Wegener's granuloma with vasculitis and Stewart's granuloma without vasculitis. In contrast Burston [4] did not accept midline granuloma as a specific entity, and showed that persistent investigation of patients in this category often resulted in a specific alternative diagnosis.

In 1966, Eichel *et al.* [5] reported 7 patients with "midline granuloma" who were subsequently diagnosed as lymphoma. Repeated biopsy was required to make the diagnosis; 5 cases were classed as "polymorphic reticulosis", 1 was called Hodgkin's disease. The polymorphic cellular content led the authors to regard the lesion as an abnormal proliferation rather than a true neoplasm. In 1977 Michaels and Gregory [6] reviewed histological material from 30 cases with nasal ulceration. Clinically the cases were a mixture of Stewart's and Wegener's "granuloma". On review, 17 biopsy specimens were classed as inflammatory, some showing evidence of vasculitis. All the Wegener's cases fell into this inflammatory category. 3 cases were clearly lymphoma, and the remaining 10 showed extensive necrosis and the presence of atypical cells in the inflammatory exudate. The authors coined the term NACE—necrosis with atypical cellular exudate—for this appearance, and felt that the atypical cells were probably some form of histiocytic lymphoma.

In 1982 Aosaza [7, 8] examined biopsies from 19 cases which had the clinical features of lethal midline granuloma. 11 showed the polymorphic pattern described by Eichel, but many cases became more monomorphic as the disease progressed. Enzyme analysis indicated that the abnormal cells were histiocytic, and the autopsy findings in 10 cases resembled those of malignant histiocytosis. Ishi *et al.*, in 1982 [9] carried out immunofluorescence on 6 cases of midline granuloma and showed the abnormal cells to stain as T-cells in 3

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cases. In 1987 Chan *et al.* [10] reported a high occurrence of T-cell neoplasms in the nose and nasopharynx and Lippman *et al.* [11] identified a T-cell phenotype in a case of "lethal midline granuloma". In an immunohistochemical study of 12 cases of midline granuloma from the files of the Institute of Laryngology and Otology in London in 1988, Ramsay *et al.* [12] reported that 10 cases showed a T-cell phenotype.

Subsequent work confirmed that many patients presenting with the clinical features of lethal midline granuloma suffered from an underlying T-cell neoplasm [13, 14]. One published study reported a possible link with Epstein–Barr virus infection [8]. This data has recently been confirmed by other authors [15, 16]. It is now clear that this nasofacial T-cell lymphoma is distinct from the usual peripheral T-cell lymphoma and typically presents as relentless ulceration of the midfacial region producing the condition which Stewart described as lethal midline granuloma.

CLINICAL AND PATHOLOGICAL FEATURES

Patients with nasofacial T-cell lymphoma present with destruction of the external nose, nasal cavity, soft palate, hard palate and nasopharynx that progresses in a relentless fashion (Fig. 1). Soft tissues, bone and cartilage are slowly destroyed in what has been described as "a wave of granulation tissue advancing irregularly into healthy parts, breaking down behind as it advanced in front, so that there was never any great depth of pathological growth present" [17]. Death can occur from haemorrhage, intercurrent infection, or cachexia, and there may be no evidence of systemic lymphoma at autopsy. A percentage of cases develop disseminated disease in the later stages [11, 24]. The reported age of affected patients ranges from 10 to 87 years [18, 19]. The youngest case in the authors' personal experience was a 9 year old boy who presented after a long history of recurrent facial and orbital cellulitis (Holgate CS, personal communication). A marked male predominance is reported in several studies [14, 24].

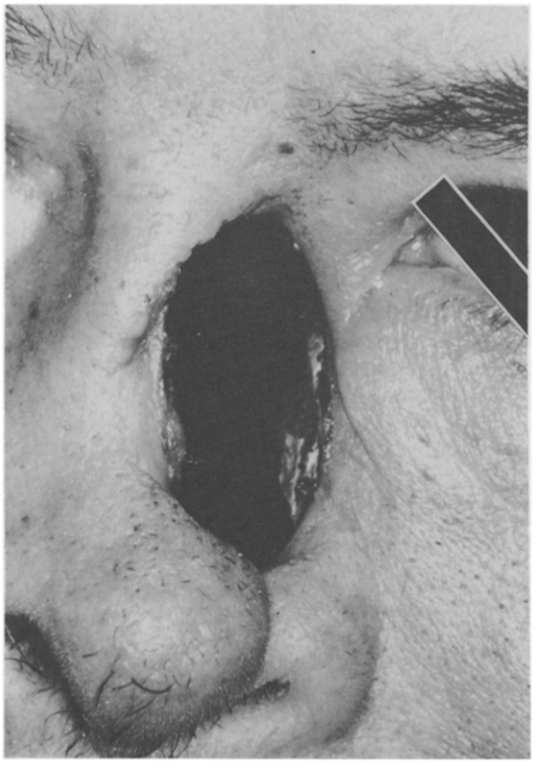

Fig. 1. Extensive destruction of the left nasal deep tissues by nasofacial T-cell lymphoma. (Photograph courtesy of Professor L Michaels, Institute of Laryngology and Otology London.)

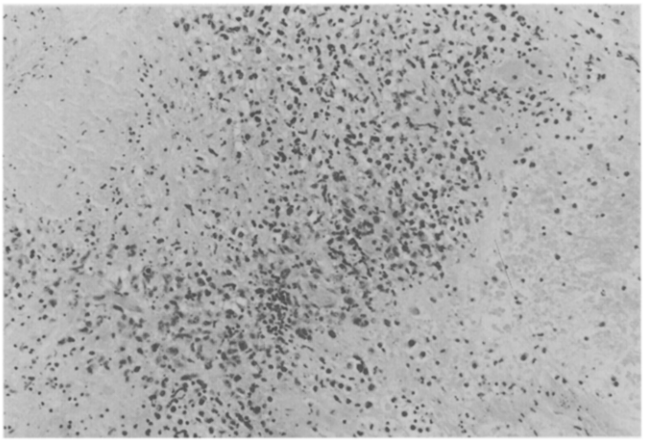

Fig. 2. Necrosis and a mixed cellular infiltrate is common in nasofacial T-cell lymphoma. Haematoxylin and eosin, ×35.

Microscopic examination of the affected tissues shows extensive coagulative necrosis of normal structures with associated inflammation and granulation tissue formation (Fig. 2). In superficial biopsies there may be no evidence of a neoplastic process, and deeper tissue samples are frequently required for a positive diagnosis. Diagnostic specimens contain a mixed (polymorphic) infiltrate composed of neutrophils, plasma cells, macrophages, small lymphocytes and atypical lymphoid cells. The latter are medium-sized or large cells that often have clear cytoplasm and show irregular nuclear outlines (Fig. 3). Some have prominent nucleoli and resemble immunoblasts or mononuclear Reed–Sternberg cells. The atypical cells frequently show an angiocentric and angiodestructive pattern of infiltration; blood vessel walls are invaded and destroyed, and there may be evidence of associated thrombosis (Fig. 4). The blood vessel involvement is responsible for the extensive necrosis that accompanies this condition. Erythrophagocytosis is seen in some cases, and the infiltrate can be seen to invade and destroy mucosal seromucinous glands [10]. Immunohistochemical studies reveal that the abnormal cells stain with T-cell antigens including CD45RO (UCHL1), CD43 (MT1), and CD3. CD30 staining is seen in a percentage of cases [12]. In cryostat sections the atypical cells stain with CD2, CD5 and CD3, and show variable CD4 and CD8 expression [13, 14]. Immunohistochemistry also shows a large background macrophage population, a feature that may have been responsible for the previous histiocytic designation of this condition. There is little data on the molecular biology of nasofacial T-cell lymphoma; Khan *et al.* could not detect a clonal rearrangement of the T-cell receptor or immunoglobulin genes in their case [20]. Further gene rearrangement studies of this condition are still awaited.

THE NON-SPECIFIC NATURE OF LETHAL MIDLINE GRANULOMA

Much of the confusion in the history, diagnosis and treatment of nasofacial T-cell lymphoma relates to the fact that

many pathological conditions can produce the clinical picture of midfacial destruction termed "lethal midline granuloma". Stewart's original cases were heterogeneous, and Michaels [21] stresses that "to categorise an ulcerating nose as midline granuloma on the basis of a non-specific chronic inflammatory infiltrate is a disservice to the patient". The list of non-lymphomatous conditions that can give rise to nasofacial ulceration includes infections (syphilis, actinomycosis, mucormycosis, tuberculosis, leishmaniasis), vasculitis (Wegener's granulomatosis), sarcoidosis and non-lymphoid neoplasms (squamous cell carcinoma, adenocarcinoma, undifferentiated nasopharyngeal carcinoma, histiocytosis X, malignant melanoma). Any patient with a destructive midline lesion should therefore be fully investigated using clinical, radiological and laboratory methods. Categorising a case as "lethal midline granuloma" when biopsies show non-specific chronic inflammation is both unwarranted and unhelpful.

RELATED CONDITIONS

In 1972 Liebow described lymphomatoid granulomatosis (LYG), a condition characterised by a polymorphic infiltrate in the lungs associated with prominent tissue destruction [22]. The infiltrate in LYG consists of a mixture of inflammatory cells and atypical lymphoid cells and frequently shows an angiocentric arrangement. Although the disease is predominantly pulmonary, lesions with the same histological pattern can also be seen in the skin and nervous system. At least 20% of cases develop into systemic lymphoma, at which time biopsies show monomorphic sheets of atypical lymphoid cells [23]. The similarity between LYG and polymorphic reticulosis was noted by DeRemee *et al.*, in 1978 [24], and later by Stamenkovic *et al.* [25], both of whom speculated that these were two forms of the same condition. Studies indicated that both disorders were due to abnormal proliferations of T-cells [10, 26, 27] and Jaffe [28] later introduced the concept of the angiocentric immunoproliferative lesion to encompass both of these entities and angiocentric T-cell lymphoma [28, 29]. Nasofacial T-cell lymphoma therefore shares features with both LYG and angiocentric T-cell lymphoma, and may be regarded as a localised form of the latter condition. The close relationship between nasofacial and angiocentric lymphoma is illustrated by cases such as that reported by Khan *et al.* in 1991 [20], where angiocentric lymphoma produced extensive ulceration and destruction of in the region of both parotid glands rather than in the nasal and midfacial area.

RESPONSE TO TREATMENT

Given the relative rarity of the condition and the range of classifications and therapeutic measures applied to nasofacial T-cell lymphoma in the past, it is difficult to obtain good data on the best treatment methods and survival rates. In cases collected over a 30-year period Ramsay *et al.* [12] recorded an overall length of survival from time of diagnosis that ranged from 3 months to 14 years. Local low-dose radiotherapy was the treatment of choice in cases diagnosed prior to 1980, when there was reluctance to make a definite diagnosis of lymphoma. This usually led to local recurrence of disease within 6 months. Similar findings are reported by Ho *et al.* [14] who reported recurrence in 4 out of 5 patients with polymorphic reticulosis treated with low dose radiotherapy (1000–2000 cGy) prior to 1978. Cases treated with combination chemotherapy regimes, with or without adjuvant radiotherapy appear to have a better overall survival rate than patients with conventional lymphomas, although local recurrence is relatively common [14]. More information is available on angiocentric T-cell lymphoma. Lipford *et al.* [29] sub-divided this condition into grades I, II and III based on the pathological features. Grade I showed a polymorphic pattern and lacked significant atypia; grade II showed polymorphism, atypia and necrosis; grade III showed an increasing monomorphic population of atypical cells. Cases categorised as grade I and II received single-agent chemotherapy (usually cyclophosphamide), grade III lesions were treated with multiple-agent chemotherapy. The overall prognosis was excellent with 15 of 23 patients classed as long-term survivors (alive with no evidence of disease at a minimum of 2 years after presentation). The grade III lymphomas treated with combination chemotherapy showed better results than the grade I and II categories, and the authors suggested that patients in these groups should have received more aggressive treatment.

Although it is difficult to draw definite conclusions from the sparse data available, the local nature of the disease suggests that nasofacial T-cell lymphoma has a better prognosis than other peripheral T-cell neoplasms and conventional nodal B-cell tumours. Treatment with combination chemotherapy

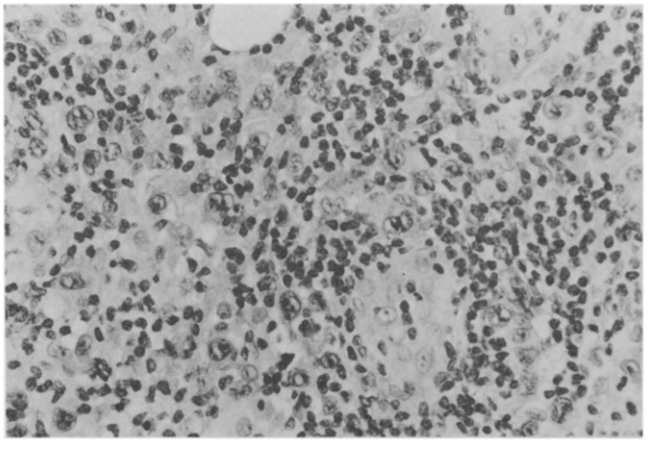

Fig. 3. Pleomorphic large cells may be seen amongst the infiltrate. Haematoxylin and eosin, ×90.

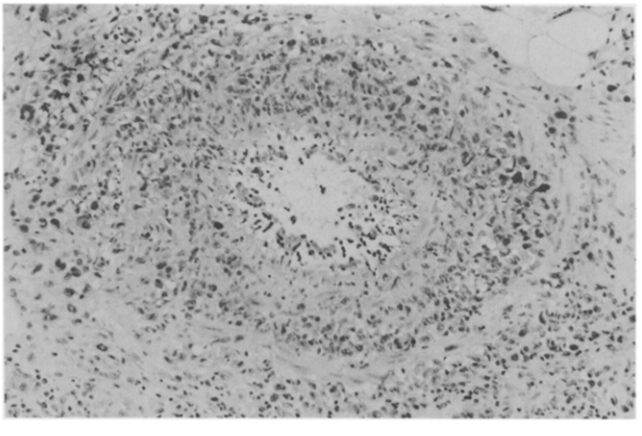

Fig. 4. Infiltration of vessels may be seen, no doubt contributing to the extensive necrosis seen in Fig. 1. Haematoxylin and eosin, ×35.

at the outset is recommended, and the use of adjuvant radiotherapy to control local disease can result in long-term disease-free survival.

SUMMARY

Since its "recognition" by Stewart in 1933 this site-specific variety of T-cell lymphoma has perplexed and fascinated pathologists and clinicians alike. The description of locally indolent B-cell lymphomas arising from mucosa-associated lymphoid tissue (MALT) in sites such as the stomach [30] has led to speculation that nasofacial T-cell lymphoma represents the T-cell equivalent of a MALT lymphoma. Whether the neoplasm arises from a malignant transformation of local T-cells or is a result of neoplastic T-cells homing onto specific receptors in the nasal tissues—possibly associated with the nasal vasculature—remains to be seen. The reports of Epstein–Barr virus DNA in cases of nasofacial T-cell lymphoma [13, 15, 16] suggests that the condition may be one of the expanding list of Epstein–Barr virus-associated malignancies.

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