Treatment of natural killer/T-cell lymphoma

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Introduction

NK (natural killer) neoplasm is rare and extranodal NK/T-cell lymphoma, nasal type, is the commonest NK cell neoplasm. Historically, different names have been used to describe this extraordinary nasal lesion. It has been called lethal midline granuloma, midline malignant reticulosis and polymorphic reticulosis.[1-4] The lesion was not specifically categorized in the previous lymphoma classification systems: Rappaport, Kiel or Working Formulation. In the REAL Classification, it has been called angiocentric lymphoma but angiocentricity is by no means pathognomonic of NK neoplasms.[5] In the Revised WHO classification, two NK neoplasms are described: extra-nodal NK/T-cell lymphoma, nasal type and aggressive NK cell leukaemia.[6,7]

Epidemiology and pathology of extra-nodal NK/T-cell lymphoma, nasal type

The tumour affects predominantly the nasal region with a peculiar pattern of extra-nasal involvement.[8,9] There is a unique geographic distribution. It affects mainly populations in the Eastern and South-eastern Asia and the Central and South America. It is rare in the West, South Asia, Middle East and Africa. Histologically, the tumour is characterized by a pleomorphic cellular infiltrate with variable cytology. There is usually prominent vascular invasion and occlusion by tumour cells, resulting in marked tissue ischaemia and necrosis.[6] Immunophenotypically, the tumor cells are CD56 positive, surface CD3 negative but cytoplasmic CD3 epsilon positive.[6] The T-cell receptor gene is usually germ-line. EBV infection is almost always demonstrable by *in situ* hybridization.[6] Clonal Epstein Barr virus (EBV) infection is consistently associated with this tumour and appears to play an important pathogenetic role.[10-14] Therefore, EBV is potentially a good tumour marker for primary diagnosis, detection of occult dissemination, disease monitoring and prognostic determination. Cytogenetic and molecular genetic studies of the tumour fail to demonstrate specific cytogenetic abnormality or mutation.[15-21] There is a suggestion that some tumour suppressor genes are involved and may be important in the pathogenesis.[17,20]

Clinical features of extra-nodal NK/T-cell lymphoma, nasal type

Clinically, there is a strong male predominance of 3 to 1. Compar-

ed with other non-Hodgkin's lymphoma, the age of the patients is relatively young. Their median age is in the fifth decade.[22-24] The tumour primarily affects nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx and larynx. It has to be distinguished from other lymphomas of the Waldeyer's ring and paranasal sinsuses, which are typically a diffuse large B-cell lymphoma.[25]

Nasal NK/T-cell lymphoma may extend locally to orbit and hard palate. Systemic dissemination is usually late. Common metastatic sites include skin, gastrointestinal tract and genital organs.[26,27] Central nervous system involvement is uncommon. Bone marrow is not commonly involved but occult involvement may sometimes be detectable by in-situ hybridization for EBV DNA. Pancytopenia may be observed as the result of haemophagocytosis.

Patients usually present with a nasal mass, nasal obstruction and bleeding. Other presenting symptoms include hoarseness of voice, dysphagia, proptosis, ophthalmoplegia, halitosis, airway obstruction and dysphonia.

In a smaller proportion of the patients, the tumour may affect primarily an extra-nasal site, such as skin, gastrointestinal tract and genital tract, a pattern similar to the metastatic sites of primary nasal tumour. For these patients, a careful examination of the nose may detect occult nasal involvement.

The Ann Arbor staging is unsatisfactory for this nasal tumour. A staging system for sinonasal B-cell lymphoma has been recommended. The International Prognostic Index initially derived for diffuse large B-cell lymphoma appears to be also useful for this tumour.[27,28] Other prognostic indexes have also been designed and used, such as the Prognostic Index for Mature T-cell lymphoma and the Korean Prognostic Index designed specifically for NK-cell lymphoma.[28]

Assessment of patients with extra-nodal NK/T-cell lymphoma, nasal type

History and physical examination reveal symptoms and signs of nasal and extra-nasal involvement by the tumour. An evaluation by an experienced otorhinolaryngologist is essential. A flexible nasal endoscopy should be performed and multiple biopsies be obtained from involved and suspicious areas. Because of the anatomical site and the intrinsic property of the tumour, the biopsy specimens are often small and necrotic, making accurate pathological interpretation challenging. A high index of suspicion is essential and repeated biopsies are often necessary. The specimen should be sent frozen instead of in formalin for optimal analysis. Adequate immunophenotyping studies are essential, and EBV study and T-cell receptor gene analysis are useful.[28]

Computerized tomography (CT) is conventionally used to assess the extent of local tumour invasion and also to detect distant metastasis. Magnetic resonance imaging (MRI) however may define local soft tissue involvement better and distinguish tumour infiltration from infection.[29] Positron emission tomography may also define well the tumour margin and detect systemic involvement.[30] Optimal imaging is critical for subsequent radiotherapy planning and is also useful for monitoring of response to therapy.

EBV infection is consistently associated with NK-cell neoplasm. The tumour may release EBV DNA into the circulation. This is mediated through apoptosis of proliferating tumour cells. Quantification of circulating plasma EBV DNA by real-time Q-PCR may serve as a surrogate marker of tumour load. This may have prognostic implication.[14] Also, the test is potentially useful for monitoring of response to therapy and detection of tumour relapse.[14]

Management of extra-nodal NK/T-cell lymphoma, nasal type

For patients with localized disease, radiotherapy has an important role to play. Careful planning with the assistance of CT or MRI is essential.[31-36] A high therapeutic dose of 50-55 Gy is recommended. The overall response rate is 60-100%. Radiotherapy appears to be superior to chemotherapy alone for localized lesions. However, there is still a high relapse rate of about 50% following radiotherapy. Most of the relapses are local. Combined chemotherapy and radiotherapy is usually recommended. An anthracyclines-containing regimen is usually used but it appears that anthracyclines may not be essential. It has been shown that L-asparaginase is a very useful drug for NK-cell tumour.[37] L-asparaginase containing regimen is now in clinical trial. Preliminary results using the SMILE regimen, which contains steroid (dexamethasone/prednisolone), methotrexate, ifosfamide, L-asparaginase and etoposide, are encouraging.[38]

For patients with advanced and disseminated disease, combination chemotherapy is the mainstay of treatment, supplemented by local radiotherapy.[31-36] Unfortunately, the clinical outcome is usually poor. Instead of using the anthracylines-containing regimens, the L-asparaginas-containing protocols are being tested.[37,38] New agents are also being explored.[39] Autologous haematopoietic stem cell transplantation has been used for treating this tumour. When performed for patients in first remission, it appears to benefit the high risk patients.[40] However, when performed for relapsed or refractory tumours, the results are disappointing.[40-41] Allogeneic transplantation has the theoretical advantage of graft versus lymphoma effect. Fifty per cent of the patients have sustained remissions after allogeneic transplants. However, the transplant related mortality is high.[42]

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