NATURAL KILLER CELL MALIGNANCIES: CLINICOPATHOLOGICAL FEATURES, DIAGNOSIS AND TREATMENT

Y.L. Kwong, Professor, Division of Haematology / Oncology and Bone Marrow Transplantation, Queen Mary Hospital, Hong Kong

The treatment of lymphoid malignancies should be planned carefully and tailored to the specific category of malignancy which has to be carefully assessed by histological, immunohistochemical, flow cytometry and other techniques. Treatment of malignancy of natural killer cells is no exception. Natural killer (NK) cells were first recognised over a decade ago during the course of studies on cell-mediated cytotoxicity.[1] Initially, NK cells were defined functionally as cytolytic cells capable of lysing target cells without prior specific immunisation or major histocompatibility complex (MHC) restriction. The target cells lysed by NK cells include tumour cells, and cells infected with bacteria and viruses.[1] Morphologically, NK cells are lymphoid cells with abundant pale cytoplasm that contains azurophilic granules (Figure 1A) and they account for about 10% of circulating blood lymphocytes.

THE IMMUNOPHENOTYPE OF NK CELLS

Although NK cells were originally defined functionally, it is now known that some subtypes of T cells also exhibit NK-like cytolytic activities. Therefore, NK cells are now better identified immunophenotypically by a specific pattern of antigen expression.[2]

CD3

NK cells do not express the surface antigen CD3, which is a marker of T cells. This is the main feature that distinguishes NK cells from T cells. However, NK cells do express the cytoplasmic epsilon (ε) chain of CD3[2], which can be detected with a polyclonal antibody.[3,4] Therefore, NK cells are surface CD3- but cytoplasmic CD3ε+.

CD56

NK cells characteristically express surface CD56. CD56, also known as N-CAM (neuronal cell adhesion molecule), is a surface glycoprotein expressed on NK cells and neural /neuroendocrine tissues.[5] It belongs to the immunoglobulin superfamily of adhesion molecules, which include the T cell receptor, CD3, MHC class I and the immunoglobulin (Ig) molecules.[6] CD56 is by far the most useful marker of NK cells.[1,2] However, CD56 is also expressed by a subfraction of T lymphocytes that mediate NK cell-like cytotoxicity.

CD16

CD16 is a low affinity receptor for the Fc region of IgG.[7] It is expressed in about 90% of normal NK cells, but is also expressed on other cell types, including granulocytes and macrophages.

CD57

CD57 is an antigen expressed by 50-60% of NK cells. As it is also expressed on non-NK lymphocytes, CD57 expression is not as reliable a marker of NK cells as CD56 and CD16.[8]

NK cell receptors

NK cells do not express clonally rearranged T cell receptor or Ig gene. They express, however, receptors for MHC class I antigens[9] which can be divided into two groups: CD94 that is dimerised with the NKG2 family of proteins, which belongs to the C-lectin superfamily of adhesion molecules; and CD158a and CD158b, which belong to the immunoglobulin superfamily. These receptors are expressed on normal NK cells, and their binding to their respective ligands mediates inhibition of NK cell function. It has been proposed that the CD94/NKG2 receptors are a more ancestral type of MHC class I recognition strategy than the CD158a/CD158b receptors that may have evolved later to provide a more refined system of MHC recognition.[10]

T cell antigens

Because NK cells may have a common ontogeny with T cells, they also express the T cell antigens CD2 and CD7, but not CD5. The TCR protein is also not expressed.[2]

TABLE 1
Clinicopathological features of nasal NK cell lymphoma, non-nasal NK cell lymphoma, and NK cell lymphoma / leukaemia

	Nasal NK cell lymphoma	Non-nasal NK cell lymphoma	NK cell lymphoma/leukaemia
Sex	M > F	M > F	M > F
Median age	50-60 years	50-60 years	30-40 years
Site	Nasal, upper aerodigestive tract	Gastrointestinal tract, skin, testis, muscle	Disseminated, liver, spleen, bone marrow
Histology and Immunophenotyping	Variable cell size, angiocentricity, necrosis, CD3-, CD3ε+, CD56+	Variable cell size, angiocentricity, necrosis, CD3-, CDε+, CD56+	Monotonous malignant cells, infiltration of involved solid organs shows angiocentricity and necrosis, CD3-, CDε+, CD56+
TCR	Germline	Germline	Germline
EBV	Most cases, clonal	Most cases, clonal	Most cases, clonal
Prognosis	Poor, median survival < 12 months	Poor, median survival < 4 months	Very poor, median survival < 2 months

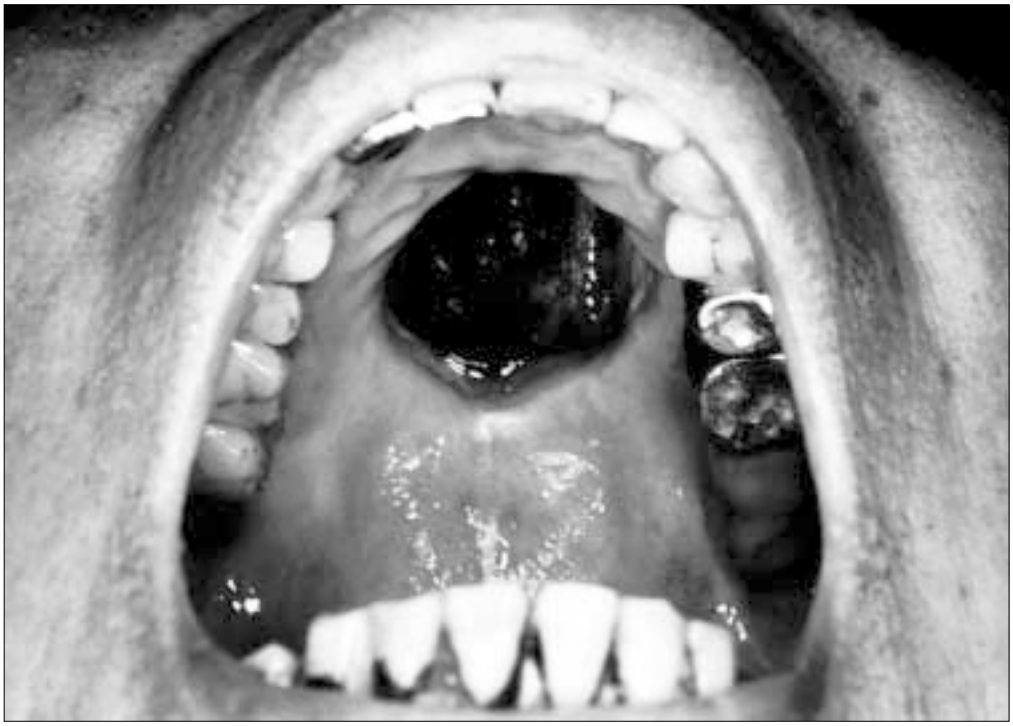

FIGURE 1A
Perforation of the hard palate leading to an oral communication with the nasal cavity, due to an extension from a nasal CD56+ NK cell lymphoma. This lesion used to be referred to in the past as a 'lethal midline granuloma'. (Reproduced with permission, John Wiley & Sons Ltd, *Hematol Oncol* 1997; 15:71-9.)

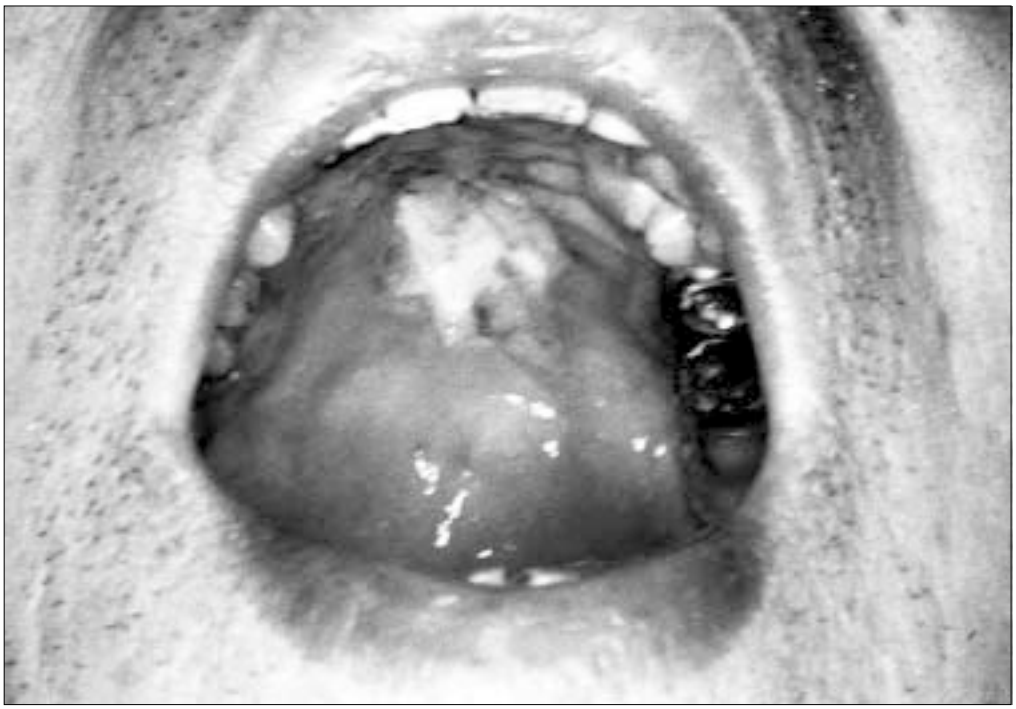

FIGURE 1B
The same patient after completion of chemotherapy and involved field radiotherapy, showing healing of the lesion by granulation.

Cytolytic markers

Several cytolytic effector molecules, including perforin and granzymes, are expressed in NK cells.[11,12] However, these molecules are also expressed in CD8+ cytolytic T lymphocytes.

Therefore, the typical immunophenotype of NK cells is CD2+, CD3-, CD3ε+, CD5-, CD7+, CD16±, CD56+, CD57±, CD94+, CD158a+, and CD158b+ (Table 1).

ONTOGENY OF NK CELLS

Recent studies have indicated that NK cells and T cells may originate from a common pluripotential stem cell.[2] In the fetal thymus, a bipotential T / NK precursor cell capable of differentiating into T and NK cells can be identified. In the adult, the bone marrow is the main site of NK cell development. Primitive NK cell precursors may be CD34- or C34+. Further development leads to the loss of CD34, and the expression of CD7 and cytoplasmic CD3ε.

MALIGNANCIES ARISING FROM NK CELLS

Lethal midline granuloma, polymorphic reticulosis and nasal lymphomas

Lethal midline granuloma, polymorphic reticulosis and various other terms (including progressive lethal granulomatous ulceration, non-healing granuloma, and the midline malignant reticulosis) have been used in the past to refer to a group of malignant, destructive lesions involving the midline facial structures (Figures 1A and 1B).[13-15] The nasal and upper aerodigestive tract (e.g. nasopharynx, oropharynx, palate and larynx) are common sites affected. Immunohistochemical studies of these tumours have revealed their lymphoid nature,[16,17] so that they should now be classified as lymphomas.

Histologically, these lesions are characterised by a polymorphic lymphoid infiltrate, associated with angiocentricity and necrosis.[18] Angiocentricity refers to the preferential concentration of tumour cells around and within blood vessels, with infiltration and destruction of the blood vessel wall (Figure 2). This peculiar pattern of infiltration led to the classification of these tumours together with other lymphomas, such as lymphomatoid granulomatosis, as angiocentric immunoproliferative lesions (AIL). The tumour cells may vary from being of a small to large size, and are often mixed with reactive inflammatory cells including lymphocytes, histiocytes, polymorphneutrophils, eosinophils and plasma cells. Features that distinguish this infiltrate from reactive conditions include the nuclear atypia of the tumour cells and the high frequency of mitotic figures.

Most lethal midline granulomas and nasal lymphomas are NK cell lymphomas

With the advent of immunophenotyping, many of the lethal midline granulomas and nasal lymphomas have now been shown to be of NK cell origin, with an imunohistochemical profile of CD2+, surface CD3-, cytoplasmic CD3ε+, and CD56+, and the TCR gene in germline configuration.[19-22] These lymphoma cells are consistently infected by the Epstein-Barr virus (EBV), which can be demonstrated by *in situ* hybridisation (ISH) with EBV encoded small nuclear RNA (EBER) probes.[22] The diagnosis of these tumours relies on a careful histological evaluation, and immunohistochemical studies to distinguish them from reactive conditions. This is facilitated by the development of a monoclonal antibody against CD56 that works on paraffin sections after appropriate antigen retrieval techniques.[23] Together with EBER ISH demonstration of EBV infection, a correct diagnosis of NK cell lymphoma should be achievable in routine diagnostic laboratories.

NK cell lymphomas of non-nasal tissues

Lymphomas of NK cell lineage have also been described outside the upper airways.[24-29] They typically involve

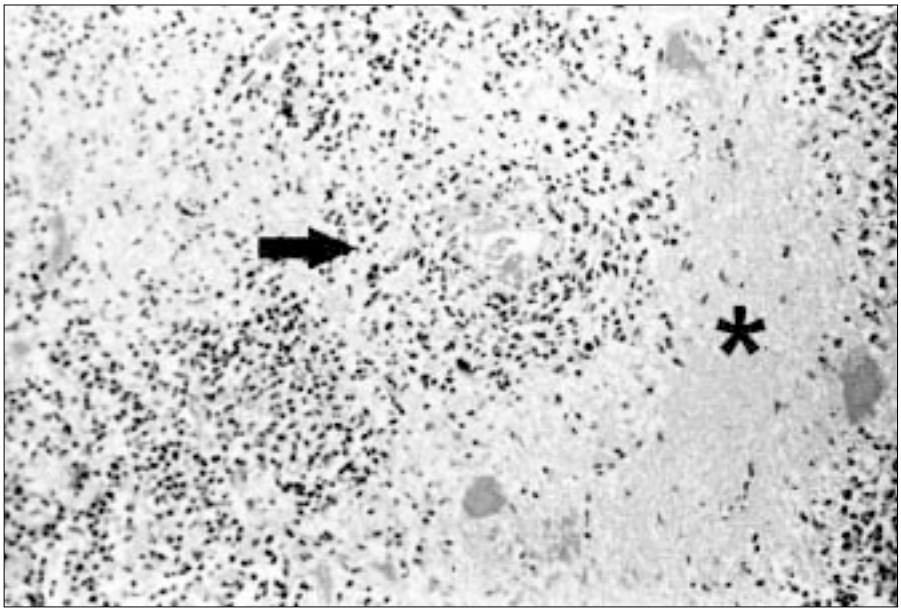

FIGURE 2

Histological appearance of an extranodal non-nasal NK cell lymphoma, showing angiocentricity with neoplastic cellular infiltration around a blood vessel (arrow), and necrosis (star). (Reproduced with permission, Blackwell Science Ltd, *Br J Haematol* 1997; 97: 821-29.)

extranodal sites including the skin, liver, spleen, gastrointestinal tract, testes and muscle. The histological, immunohistochemical, genotypic and EBV infection profiles are identical to those of the nasal counterparts, so that these tumours are referred to as non-nasal NK cell lymphomas.

NK cell leukaemia

A particularly aggressive type of NK cell malignancy with disseminated organ involvement and a leukaemic phase was first reported by Fernandez *et al.*[30] and subsequently by many other groups.[27,28,31-33] The clinical picture is typically fulminant. Patients present with high fever, impaired liver function, pancytopenia, and infiltration of the liver, spleen, lymph nodes, bone marrow and skin. Circulating leukaemic cells have the morphology of large granular lymphocytes, and haemophagocytosis can readily be observed in the marrow and occasionally in the peripheral blood.[27] The histological, immunohistochemical, genotypic and EBV infection profiles are identical to those of the nasal NK cell lymphomas. NK cell leukaemia has a grave prognosis and a virtually uniform mortality, with the patients dying within days to weeks of presentation. These cases must be distinguished from T-large granular lymphocyte leukaemia that is of T cell origin (CD3+), which runs a chronic course, and from NK cell lymphocytosis that is an indolent disease.

THE PATHOLOGY OF NK CELL LYMPHOMA / LEUKAEMIA

The clinicopathological features of different types of NK cell lymphomas / leukaemias are summarised in Table 1. Tumour cells vary from small, medium to large in size, with angioinvasion, angiodestruction and necrosis often seen. Haemophagocytosis is frequently observed in the liver and bone marrow, and occasionally in the peripheral blood. In imprints of involved tissues, some malignant cells may resemble large granular lymphocytes with azurophilic granules.

DISEASES THAT MUST BE DISTINGUISHED FROM NK CELL LYMPHOMA / LEUKAEMIA

T cell lymphomas

Surface expression of the antigen CD3 is a diagnostic hallmark of T cell lymphomas. Although NK cell lymphomas do not express surface CD3, they do express cytoplasmic CD3ε that can be picked up by polyclonal anti-CD3 antibodies that work on paraffin sections.[3] For this reason, if immunohistochemical studies are only carried out on paraffin sections, NK cell lymphomas and peripheral T cell lymphomas cannot be differentiated from one another. Therefore, to make a confident diagnosis, one needs to demonstrate the absence of surface CD3 expression either on frozen section or by flow cytometry in NK cell lymphoma, and the presence of surface CD3 expression in T cell lymphoma. If molecular genetic analysis can be performed, the TCR gene should be in germline configuration in NK cell malignancies, and clonally rearranged in T cell lymphomas. True T cell lymphomas of the nasal area shows less systemic dissemination and a slightly better outcome, although it is still considered a poor prognostic category of non-Hodgkin's lymphoma.[29]

T large granular lymphocyte leukaemia

T large granular lymphocyte leukaemias (T-LGLL) are chronic indolent diseases marked by anaemia, neutropenia and recurrent infections.[34] Pure red cell aplasia develops in some patients. They should readily be differentiated from NK cell malignancies, as they are *bona fide* T cell malignancies with expression of T cell markers including CD3 and usually CD8, and have TCR clonally rearranged. In most cases, EBV infection is not present. Occasionally, T-LGLL may also express CD56.

Chronic NK cell lymphocytosis

Chronic NK cell lymphocytosis is a rare disorder in which there is a persistent increase in circulating NK cells that are CD3-CD16+. The status of CD56 has not been extensively investigated.[35] The TCR gene should be in germline configuration. Clinically, it is an indolent disease, and patients present with neutropenia, vasculitis and occasionally pure red cell aplasia. Owing to a lack of clonal markers it is unknown if they are reactive or neoplastic in nature.

THE MOLECULAR PATHOLOGY OF NK CELL LYMPHOMA / LEUKAEMIA

Conventional karyotypic analysis

Conventional karyotypic analysis of NK cell malignancies is difficult, partly owing to the necrosis and scarcity of the clinical samples. However, several chromosomal abnormalities have been defined in a limited number of patients.[36,37] The most consistent one appears to be deletion of the long arm of chromosome 6 (6q-). With combined immunophenotyping and fluorescence *in situ* hybridisation, 6q- has been shown to be localised to NK cells, demonstrating the neoplastic nature of these cells.[38]

Comparative genomic hybridisation

Comparative genomic hybridisation (CGH) is a recently developed molecular cytogenetic technique that examines global genomic imbalances in tumours. With CGH, a high degree of genomic imbalance has been defined in NK cell malignancies, showing that these tumours are highly unstable genetically. Consistent patterns of chromosomal gains or losses have been defined,[39] and may be targets for further molecular analysis.

Molecular genetics

The molecular mechanisms leading to the malignant transformation of NK cells remain undefined. However, one almost invariable association is infection of the tumour cells by EBV. It has been shown that EBV is present as a single episomal form localised to the neoplastic cells.[40] This is consistent with infection of a single tumour precursor cell that subsequently gives rise to the neoplastic clone, implying that the EBV may play an important role in tumour pathogenesis. Molecular examination has also shown that the EBV infected tumour cells downregulate the expression of immunogenic EBV antigens including EBNA2 – EBNA6. This implies that the neoplastic cells may escape from surveillance by cytotoxic T cells.[41]

EPIDEMIOLOGY OF NK CELL LYMPHOMA / LEUKAEMIA

Geographical variation in the incidence of NK cell lymphoma / leukaemia

Although NK cell lymphoma / leukaemia are uncommon malignancies, they are found much more in Oriental than in Occidental patients. To date, of about 180 cases of NK cell malignancies reported worldwide, over 80% were described in Chinese and Japanese patients.[24,25,27-29,31,42] A

small number were also reported from South America.[43] This distinct geographical difference is intriguing. A genetic susceptibility to EBV-induced cellular transformation may be possible. This is supported by a very high incidence of nasopharyngeal carcinoma in Oriental patients, a malignancy that is again invariably associated with EBV infection of the tumour cells.

TREATMENT AND PROGNOSIS OF NK CELL LYMPHOMA / LEUKAEMIA

NK cell malignancies are highly malignant and the prognosis is amongst the worst of the non-Hodgkin's lymphomas. The treatment of NK cell lymphoma / leukaemia has been unsatisfactory so far. Conventional anthracycline-containing regimens have resulted in poor complete remission rates and short survivals. The median survivals in three series have been 3.5, 11 and 12.5 months.[27-29] Conventional lymphoma staging does not appear to have a major impact on survival. On the other hand, in nasal NK cell lymphoma, the degree of local destruction appears to be prognostically important.[44] For nasal and non-nasal NK cell lymphomas, anthracycline-containing combination regimens should be used, followed by irradiation of the involved field. In view of the poor prognosis, high dose chemotherapy and autologous stem cell transplantation are offered to patients who achieve complete remission;[45] this is usually feasible as the marrow is often not involved initially. For patients presenting with NK cell lymphoma / leukaemia similar aggressive therapies should be given, although as yet no successfully treated cases have been reported.

CONCLUSION

NK cell lymphoma / leukaemia is a recently defined group of aggressive malignancy with a predilection for Oriental patients. An almost invariable association with EBV infection suggests that this viral association may be pathogenetically significant. Finally, the disease has a poor prognosis, and intensive chemotherapy with stem cell rescue may be the most suitable treatment option.

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MRCP (UK) PART 2 EXAMINATION

We wish to give you notice of changes to the MRCP (UK) Part 2 Examination in 2001 and how it will affect the arrangements for both the Written and Clinical components of the Examination. This applies to the MRCP(UK) General Medicine Examination only.

The Part 2 Written Examination will become free standing. Candidates who pass the Part 2 Written Examination will be entitled to up to three attempts at the new style clinical examination called PACES (Practical Assessment of Clinical Examination Skills) without re-entering the Part 2 Written Examination.

PACES will replace the current Oral and Clinical Examination. This was first announced in December 1999. It will be held three times a year in UK centres and, at the same diets as at present, in overseas centres. Candidates can choose when they wish to enter PACES but the three attempts allowed under the new Regulations must be made within a period of two years after passing the Part 2 Written Examination.

Success in PACES will lead to the award of the MRCP(UK) Diploma. Those failing PACES three times will be required to resit and pass the Part 2 Written Examination provided they remain eligible to do so (i.e are within seven years of having passed the Part 1 Examination), before re-entering PACES.

Information explaining PACES is available on the websites of the three Royal Colleges of Physicians and more details will be issued shortly. New application forms for the 'free standing' Part 2 Written Examination and PACES will be available shortly from all three Royal Colleges. The amended MRCP (UK) Examination Regulations will be available later this year.

Contact addresses are listed below:

Royal College of Physicians of Edinburgh
9 Queen Street, Edinburgh EH2 1JQ
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Fax: 0131 225 2053
http: //www.rcpe.ac.uk

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Tel: 0141 221 6072
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Tel: 020 7935 1174
Fax: 020 7486 4514
http: //www.rcplondon.ac.uk

MRCP(UK) Central Office
11 St Andrews Place, Regent's Park, London NW1 4LE
Tel: 020 7935 1174
Fax: 020 7487 2628

An announcement about the arrangements for the MRCP(UK) Paediatric/MRCPCH Examination m 2001 will be made shortly.

Dr K.M. Cochran
Chairman
MRCP(UK) Policy Committee
26 July 2000