

REVIEW

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Aggressive mature natural killer cell neoplasms: from epidemiology to diagnosis

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Abstract

Mature natural killer (NK) cell neoplasms are classified by the World Health Organization into NK/T cell lymphoma, nasal type (NKTCL), aggressive NK-cell leukemia (ANKCL) and chronic lymphoproliferative disorders of NK-cells, the latter being considered provisionally. NKTCL and ANKCL are rare diseases, with higher prevalence in Asia, Central and South America. Most NKTCL present extranodal, as a destructive tumor affecting the nose and upper aerodigestive tract (nasal NKTCL) or any organ or tissue (extranasal NKTCL) whereas ANKCL manifests as a systemic disease with multiorgan involvement and naturally evolves to death in a few weeks. The histopathological hallmark of these aggressive NK-cell tumors is a polymorphic neoplastic infiltrate with angiocentricity, angiodestruction and tissue necrosis. The tumor cells have cytoplasmic azurophilic granules and usually show a CD45^{bright}, CD2⁺, sCD3⁻, cytCD3epsilon⁺, CD56^{bright}, CD16^{-/+}, cytotoxic granules molecules⁺ phenotype. T-cell receptor genes are in germ-line configuration. Epstein-Barr virus (EBV) -encoded membrane proteins and early region EBV RNA are usually detected on lymphoma cells, with a pattern suggestive of a latent viral infection type II. Complex chromosomal abnormalities are frequent and loss of chromosomes 6q, 11q, 13q, and 17p are recurrent aberrations. The rarity of the NK-cell tumors limits our ability to standardize the procedures for the diagnosis and clinical management and efforts should be made to encourage multi-institutional registries.

Keywords: NK-cell Neoplasms, NK/T-cell Lymphoma, Nasal-type, Aggressive NK-Cell Leukemia, CD56

Resumo

As neoplasias de células *natural killer* (NK) maduras foram classificadas pela Organização Mundial de Saúde em três entidades: o linfoma de células NK/T tipo nasal (NKTCL), a leucemia agressiva de células NK (ANKCL) e as doenças linfoproliferativas crônicas de células NK, estas últimas consideradas uma entidade provisória. Os NKTCL e a ANKCL são doenças raras, mais prevalentes na Ásia, na América Central e na América do Sul. A maioria dos NKTCL tem uma apresentação extra-ganglionar, na forma de tumor destrutivo que atinge o nariz e o trato aerodigestivo alto (forma nasal) ou qualquer órgão ou tecido (forma extranasal). A ANKCL manifesta-se como uma doença sistêmica que evolui para a morte em poucas semanas. Do ponto de vista histopatológico, estas neoplasias caracterizam-se por um infiltrado polimórfico, com angiocentricidade, destruição vascular e necrose tecidual. As células tumorais têm grânulos azurófilos no citoplasma e o seu imunofenótipo (CD45^{forte}, CD2⁺, sCD3⁻, cytCD3epsilon⁺, CD56^{forte}, CD16^{-/+}, proteínas dos grânulos citotóxicos⁺) é característico. Os genes que codificam para o recetor das células T estão em configuração nativa. As células tumorais expressam geralmente proteínas da membrana e ARN do vírus Epstein Barr, com um padrão sugestivo de uma infecção vírica latente tipo II. As alterações cromossômicas são

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complexas, e algumas, como deleções nos braços longos dos cromossomas 6, 11 e 13 e do braço curto do cromossoma 17, ocorrem de forma recorrente. A raridade dos tumores de células NK limita a nossa capacidade para uniformizar os procedimentos de diagnóstico e a abordagem clínica, sendo necessário desenvolver esforços para promover os registos multicêntricos.

Palavras-chave: Neoplasias de células NK, Linfomas de células NK, tipo nasal, Leucemia agressiva de células NK, CD56

Introduction

Lymphoproliferative disorders of natural killer (NK) cells are rare diseases which account for less than 5% of all lymphoid neoplasms and comprise different clinical entities [1-17].

The World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, updated in 2008, has made advances in their classification. Accordingly, three disease conditions originating from mature NK-cells were proposed based on their distinct clinical and pathological features [18]. These include two aggressive mature NK-cell neoplasms – extranodal NK/T cell lymphoma, nasal type (NKTCL) [19], and aggressive NK-cell leukemia (ANKCL) [20] – and one provisional entity – chronic lymphoproliferative disorders of NK-cells (CLPD-NK) [21] (Table 1). The first two entities are indexed individually in the 10th revision of the International Classification of Diseases (ICD-10) [22] and in the 3rd edition of the ICD for Oncology (ICD-O-3) [23], as well as in Orphanet databases [24]. In addition, two diseases were proposed in the past as originating from NK-cell precursors, based mainly on the blastic appearance and the CD56⁺ immature immunophenotype of the neoplastic cells. The first, NK-cell lymphoblastic leukemia / lymphoma [25], in fact comprise an heterogeneous group of immature disorders originating from NK-, T- and/or myeloid cell precursors, and is now being considered in the group of the acute leukemia of ambiguous lineage; the other, blastic plasmacytoid dendritic cell neoplasm, previously designed blastic NK-cell lymphoma, arises from plasmacytoid dendritic cells and should no longer be considered a NK-cell malignancy [26].

Nasal type NKTCL, originates in nasal and extranasal organs and tissues and account for the majority of cases, with only exceptional cases presenting primarily in the lymph nodes. ANKCL manifests as a systemic disease with multiorgan failure and rapidly evolves to death. The diagnosis of these aggressive NK-cell neoplasms is often difficult and requires both clinical suspicion and a differentiated laboratorial approach based in morphological, immunophenotypic and molecular studies.

We review the epidemiology and the clinical and laboratorial criteria for the diagnosis of NKTCL and ANKCL, with emphasis on tissue histology and on the morphological, immunophenotypic and genetic features of the neoplastic cells.

Review

Epidemiology

Both NKTCL and ANKCL are relatively frequent in Asia, Central and South America, but extremely rare in Europe and North America [1-17].

Extranodal NK/T-cell lymphoma, nasal type, and ANKCL are relatively frequent in Central American (e.g. Mexico, Guatemala), South American (e.g. Argentina, Brazil, Peru, Chile) and Eastern (e.g. Hong Kong, Japan, Korea) countries, where they may account for up to 10% of the non Hodgkin's lymphoma (NHL), whereas very uncommon in North America and Europe, where they represent less than 1% of the NHL^a [1,2,27-29]. Moreover, in series from the United States in which the ethnic background was recorded, most patients with NKTCL were of Asian or Hispanic descent [30]. Few epidemiological data is available in Europe, where its prevalence has been estimated to be lower than 1–9 cases / 1.000.000 inhabitants.

Aggressive NK-cell neoplasms are almost always associated to Epstein Barr Virus (EBV) and similarly to that occurring in Hodgkin's lymphoma and nasopharyngeal carcinoma, the neoplastic NK-cells usually have a type II latency pattern, expression of EBV nuclear antigens (EBNA) and latent membrane proteins (LMP) being limited to EBNA-1, LMP-1, and LMP-2 [31]. In Asia, increase in the risk of developing nasal NKTCL have been described among crop producers and individuals exposed to pesticides [32], also having an increased risk to develop NHL in general [33,34].

The International Peripheral T-cell Lymphoma Project (IPTCLP) group reported a four-fold higher relative frequency of NKTCL among lymphomas in Asian countries compared to Western countries, ANKCL being rarer than NKTCL (Table 2). From the 136 cases of NK-cell neoplasms analyzed by this group, collected in different centers from various countries in North America, Europe, and Asia, only 2 (1.5%) corresponded to ANKCL, as compared to 127 cases of NKTCL, the remaining 7 cases being unclassifiable according to the WHO schema [35]. Comparatively, based on the Japanese survey of NK-cell neoplasms diagnosed from 1994 to 1998 [36], the NK-cell Tumor Study Group reported on a Japanese series of 172 NK-cell tumors, which included 22 ANKCL (12.8%) [37]. Few European series of NKTCL were published to date [38,39] and, in Europe, reports on ANKCL are limited to sporadic cases [40-43].

Table 1 Natural killer cell neoplasms according to the World Health Organization classification of tumors of hematopoietic and lymphoid tissues

WHO classification, 2008	Disease entities	Putative cells of origin	Orphanet numbers	Synonyms in the Orphanet data base	ICD codes		Prevalence categories (/1.000.000)	[References]
					ICD-10	ICD-O-3		
NK-cell neoplasms	Extranodal NK/T-cell lymphoma (NKTCL), nasal type	Mature NK-cells	86879	NK/T-cell lymphoma; Nasal T/natural killer-cell lymphoma; Angiocentric T-cell lymphoma; Lethal midline granuloma	C86.0	9719/3	<1-9	[19,22-24]
	Aggressive NK-cell leukemia (ANKCL)	Mature NK-cells	86873	Aggressive NK-cell leukemia; Aggressive NK-cell lymphoma; NK-cell LGL leukemia; NK-cell large granular lymphocyte leukemia	C94.7	9948/3	<1-9	[20,22-24]
Provisional entities	Chronic lymphoproliferative disorders of NK-cells (CLPD-NK)	Mature NK-cells	Not available	NK-cell LGL leukemia; NK-cell large granular lymphocyte leukemia (considered together with ANKCL)	Not available (C94.7)*	Not available (9831/3)**	Unknown	[21-24]
	NK-cell lymphoblastic leukemia / lymphoma	NK-, T- and/or myeloid precursor cells	Not available	Not available	Not available	Not available	Unknown	[22-25]

Abbreviations: *ICD-10* International Statistical Classification of Diseases and Related Health Problems (formerly designated International Classification for Diseases), 10th revision, 2010, World Health Organization (available in: <http://apps.who.int/classifications/icd10/browse/2010/en>; accessed in 2 February 2013); *ICD-O-3* International Statistical Classification of Diseases and Related Health Problems, for Oncology (formerly designated International Classification of Diseases for Oncology, 3rd edition, 2000, World Health Organization (available in: <http://www.who.int/classifications/icd/adaptations/oncology/en/index.html>; accessed in 2 February 2013); *WHO* World Health Organization.

Blastic plasmacytoid dendritic cell neoplasm, also known as CD4⁺ CD56⁺ hematodermic neoplasm and previously designed blastic NK-cell lymphoma (Orpha:86870; ICD-10: C86.4, still referred as blastic NK-cell lymphoma; ICD-O: 9727/3) arises from plasmacytoid dendritic cells and should no longer be considered a NK-cell malignancy [26].

* Considering the synonymous list, CLPD-NK, which include chronic NK-cell LGL leukemia cases, are considered together with ANKCL; ** According to the proposal of the WHO classification, 2008, CLPD-NK should be considered together with T-LGLL in the ICD-O.

Table 2 Frequencies of NK/T-cell Lymphoma, nasal type, and aggressive NK-cell leukemia in previous published series

Series	Origin	NKTCL	ANKCL	NKTCL + ANKCL	[References]
NK-cell Tumor Study Group *	Asia (Japan)	150 (87.2%) Nasal: 123 (82.0%) Extranasal: 27 (18.0%)	22 (12.8%)	172 (100%)	[37]
International Peripheral T-Cell Lymphoma Project (IPTCLP) group**	North America, Europe, and Asia	127 (98.5%) Nasal: 92 (72.4%) Extranasal: 35 (27.6%)	2 (1.5%)	129 (100%)	[35]
Brazilian group	South America (Brazil)	120 (100%) Nasal: 97 (80.8%) Extranasal: 23 (19.2%)	0 (0%)	120 (100%)	[44]
Intergruppo Italiano Linfomi	Europe (Italy)	26 (100%) Nasal: 23 (88.5%) Extranasal: 3 (11.5%)	0 (0%)	26 (100%)	[39]
All series		423 (94.6%) Nasal: 335 (79.4%) Extranasal: 88 (20.6%)	25 (5.6%)	447 (100%)	NA

Abbreviations: ANKTCL aggressive NK-cell leukemia, NKTCL NK/T-cell Lymphoma, nasal type, NA not applicable.

* Most of the cases presented in this series were from the Japanese survey of NK-cell neoplasms diagnosed between 1994 and 1998, in which 237 cases were registered: 149 nasal-type NK-cell lymphoma (123 nasal and 26 extranasal), 22 aggressive NK-cell leukemia/lymphoma, 19 chronic NK lymphocytosis and 57 cases corresponding to diseases that are not considered as originating from mature NK-cells accordingly to the WHO classification updated in 2008 (11 myeloid/NK-cell precursor acute leukemia, 15 blastic NK-cell lymphoma, 21 precursor NK-cell acute lymphoblastic leukemia) [36].

** Consecutive cases of peripheral T-cell lymphoma (excluding Mycosis Fungoides and Sezary syndrome) and NK/T-cell lymphoma diagnosed between 1990 and 2002. Total number of cases registered: 1153 (Asia: 464, 40.2%; Europe and North America 689, 59.8%). Total number of NK-cell neoplasms registered: 136 (11.8%) (Asia: 104, 76.5%; Europe and North America: 32, 23.5%) (NKTCL: 127; ANKCL: 2; unclassified NK-cell neoplasms: 7).

Two variants of extranodal NKTCL, have been described, the nasal and the extranasal forms, the first being more frequent in nearly all reported series. In the register from the Japanese survey, only 18% of the NKTCL were extranasal [37], a higher percentage of extranasal cases (28%) being found among the NKTCL reported by the IPTCLP group [35]; in addition, a Brazilian and an Italian series of NKTCL included 19% and 12% of extranasal lymphomas, respectively [39,44] (Table 2).

Clinical features

Extranodal NK/T cell lymphomas, nasal type

The nasal and extranasal forms of NKTCL differ from each other from the clinical point of view (Table 3) [1,10,14,45].

Nasal NK/T cell lymphomas

In contrast to that observed in Occidental countries, where the majority of the sinonasal lymphomas are B-cell

Table 3 Major clinical features of the NK-cell lymphoma, nasal type, and aggressive NK-cell leukemia

Clinical features	NKTCL (nasal)	NKTCL (extranasal)	ANKCL
Gender	Males > Females	Males > Females	Males = Females
Age (years)	50 – 60	50 – 60	30 – 40
Sites primarily involved	Nose, paranasal sinuses, orbits	Skin, gastrointestinal tract, salivary glands, lungs, eyes, soft tissues, adrenal glands, brain, breast, tongue, other organs and tissues; rarely lymph nodes.	Blood, bone marrow, spleen, liver, lymph nodes
Clinical presentation	Nasal bleeding, nasal obstruction, palate perforation, mid-facial and/or upper airway destructive lesions	Ulcers, masses	Fever, jaundice, splenomegaly, hepatomegaly, lymphadenopathy, cytopenias, hemophagocytic syndrome
Prognosis	Early stages (I/II): good Advanced stages (III/IV): poor	Usually advanced stages (III/IV): poor	Highly aggressive / fatal

Abbreviations: ANKTCL aggressive NK-cell leukemia, NKTCL NK/T-cell Lymphoma, nasal type. Adapted from [14].

lymphomas, in Asia more than 40% of these lymphomas originate from NK-cells. This neoplasm (also known as “lethal midline granuloma” or “midline malignant reticulosis”) commonly affects males and generally manifests as a localized disease, with mid-facial and/or upper airway destructive lesions [1,10,14,45]. Patients with nasal NKTCL present with nasal signals and symptoms, including mass, obstruction swelling, or bleeding. The tumor is locally invasive and often infiltrates the surrounding tissues, such as the nasopharynx, the oropharynx, the palate and the orbits; dissemination to other organs may occur in advanced disease stages.

Extranasal NK/T cell lymphomas

The extranasal form is frequently disseminated at the time of the diagnosis, most patients having multiple organs and tissues involved, usually without adenopathies [1,10,14,45]. Patients with extranasal NKTCL often have more adverse clinical features such as an advanced stage and poor performance status, and are more likely to have cytopenias, when compared to patients with nasal lymphoma [1,10,14]. The tumor may involve any anatomic site at the disease presentation or during disease progression, including the skin, the gastrointestinal tract, the testis, the lungs, the eyes, the soft tissues, the adrenal glands, the brain, the breast and the tongue [1,10,14]. The diagnosis of an extranasal NKTCL requires the exclusion of occult nasal disease, which may require nasal endoscopy with random biopsies.

Bone marrow involvement at the diagnosis is uncommon in NKTCL, in both nasal (<3.5%) and extranasal (<7%) cases [4,46]. In contrast, the hemophagocytic syndrome is relatively frequent, and often occurs in advanced disease [47].

Nodal NK-cell lymphomas, nasal type

Although nodal NKTCL are not being considered separately in the WHO classification, a few cases of NKTCL presenting primarily in the lymph nodes have been described [44,48-52]. Some of these cases were included in extranasal NKTCL series [44,50] and in series of patients with cytotoxic lymphomas [51]. For instance, in a review of 49 Asian cases of CD56+ neoplasms from which 34 were NKTCL, one had a primary nodal presentation [50] and a Brazilian series of 122 cases NKTCL, from which 23 cases were extranasal, included 6 nodal cases [44]. In another series of 66 patients with nodal cytotoxic cell lymphomas, one had the classic NKTCL phenotype [51]. In addition, cases of nodal lymphomas with a typical NKTCL phenotype and T-cell receptor (TCR) gamma (*TCRG*) gene rearrangements in germline configuration were described as case reports [48,49]. However, in other cases, the tumor probably originates from cytotoxic T-lymphocytes, as in the series of nodal

lymphoma with a typical NKTCL phenotype reported by Takashi et al., from which 4 cases had clonal *TCRG* gene rearrangements [52]. Nodal NKTCL have a poor prognosis, most patients surviving for less than one year; they usually affect the cervical lymph nodes and the histology and phenotype are similar to those of extranasal NKTCL.

Aggressive NK-cell leukemia

Aggressive NK-cell leukemia is a very rare and extremely aggressive neoplasm, also with a higher prevalence among Asians [2,35,36,53-55]. Men and women are equally affected and the disease usually manifest in the third or four decades. Patients usually present extremely ill, with fever and other systemic symptoms, hepatosplenomegaly, pancytopenia and abnormal liver function. Serum levels of lactic dehydrogenase (LDH) and Fas Ligand (FasL) are often markedly increased. The hemophagocytic syndrome is frequent at diagnosis or during the disease course, resulting from uncontrolled monocyte/macrophage activation in response to cytokines produced by the neoplastic NK-cells [56-61]. The natural disease course is fulminant, with multiorgan failure and disseminated intravascular coagulation, death occurring usually within a few weeks [62].

Clinical staging

The Ann-Arbor staging system, originally designed for Hodgkin's lymphoma, is used for clinical staging of the NHL in general (Table 4) [63,64]. However, this system is not completely satisfactory for NKTCL, as it does not take into account the tumor size and the invasion to contiguous structures, which may be important prognostic features. Consequently, a modified tumor-staging system originally proposed for sinonasal B-cell lymphoma was adopted, which takes into account the local involvement [65] (Table 4).

In order to perform disease staging, patients should be evaluated with routine hematological and biochemical analysis, bilateral bone marrow trephine biopsy, chest radiography, computerized tomography, and digestive endoscopy. In addition, magnetic resonance imaging helps to define the local involvement in nasal lymphoma, being superior to computerized tomography in determining the extent of soft-tissue infiltration, in differentiating inflamed from neoplastic tissue, and in clarifying bone lesions [66]. Positron emission tomography using fluorine-18-fluoro-deoxy-glucose is useful to investigate systemic spread and to distinguishing lymphoma from inflammatory masses [67].

The ratio of patients presenting limited extranasal disease stages (I_E or II_E) versus those with presenting with advanced disease stages (III or IV) is 7:3 for nasal NKTCL and 4:6 for extranasal NKTCL [36].

Table 4 Clinical staging systems used for aggressive NK-cell neoplasms

Staging system	Stages	Staging criteria	[References]
Ann Arbor staging system*	Stage I	Confined to one lymph node site-	[63,64]
	Stage II	Confined to more than one lymph node site but on one side of the diaphragm.	
	Stage III	Confined to lymphatic tissue or spleen but on both sides of the diaphragm.	
	Stage IV	Bone marrow or liver involvement or extranodal sites with widespread involvement.	
Tumor staging used as a complement to the Ann Arbor staging system for nasal NK/TCL	T1	Confinement to the nasal cavity.	[65]
	T2	Extension to the maxillary antra, anterior ethmoid sinus or hard palate.	
	T3	Extension to posterior ethmoid sinus, sphenoidal sinus, orbit, superior alveolar bone, cheeks, or superior buccinators space.	
	T4	Involvement of the inferior alveolar bone, inferior buccinators space, infratemporal fossa, nasopharynx, or cranial fossa.	

Abbreviations: NK natural-killer cells, NKTCL NK/T-cell Lymphoma, nasal type.

* Subscripts: A or B: absence (A) or presence (B) of constitutional symptoms; E: "extranodal" disease; X: largest tumor >10 cm large ("bulky disease"), or mediastinum wider than 1/3 of the chest on a chest X-ray; S: spleen involvement. NK/TCL are usually extranodal lymphomas; thus, the subscript E applies to the vast majority of cases.

Laboratorial diagnosis

Histology and cytology

Natural killer/T cell lymphoma, nasal type, are histologically characterized by angiocentricity and invasion of the blood vessels by lymphoma cells, resulting in ischemic necrosis; the neoplastic cells have a variable size and usually appear morphologically immature and the cytological features are heterogeneous, with a variable mixture of inflammatory cells. Azurophilic granules are usually observed in the cytoplasm of the lymphoma cells using imprint smears [6]. Aggressive NK-cell leukemia cells are larger than normal large granular lymphocytes and often have a pale or slightly basophilic cytoplasm with azurophilic granules and a nucleus with slightly immature chromatin and inconspicuous or distinct nucleoli. As in NKTCL, necrosis, apoptosis, angioinvasion, and angiodestruction are common findings in tissue biopsies [6]. Also frequent is hemophagocytosis, which results from uncontrolled macrophage stimulation by inflammatory cytokines produced by the neoplastic cells and may result in the development of a hemophagocytic syndrome.

Immunophenotype

Most of our knowledge on the immunophenotype of the neoplastic NK-cells in NKTCL [30,35,37,50,68-70] as in ANKCL [2,50,53-55,71-75], is based on immunohistochemistry studies.

Like normal NK-cells, NKTCL and ANKCL tumor cells do not express CD3 and the TCR on their surface [1]. Nevertheless, they often have the epsilon chain of CD3 in the cytoplasm and, therefore, they may stain positively for CD3 in immunohistochemistry of paraffin sections, imposing the differential diagnosis with T-cell lymphoma [30]. Also as normal NK-cells, tumor NK-cells do not rearrange

TCR genes, which can be shown to be in germ-line configuration by polymerase chain reaction (PCR) analysis. In addition, NKTCL and ANKCL tumor cells nearly always express CD2 and less often CD7 and CD8, but not CD4 and CD5. From the markers usually used to identify NK-cells, CD56 is the most frequently positive, whereas CD16 expression is variable, and CD57 is almost never found. In addition, cytotoxic granule-associated proteins such as T-cell-restricted intracellular antigen (TIA-1), granzyme B, and perforin are frequently expressed. The immunophenotypic characteristics of NKTCL and ANKCL cells seems to be similar, except for a higher frequency of cyCD3epsilon⁺ and a lower frequency of CD16⁺ cases in NKTCL [37].

Only a limited number of studies have evaluated the expression of killer receptors on the neoplastic NK-cells from patients with NKTCL and ANKCL [76-80]. Reverse transcriptase PCR techniques, revealed that most NKTCL tumor cells do express killer lectin type receptors (KLR) transcripts, including those for the CD94 and the NKG2 (most frequently NKG2A/B and NKG2D) receptors [80], a result that was confirmed by immunohistochemical stainings on tissue biopsies [76,77] and flow cytometry immunophenotyping of NKTCL and ANKCL cells [78]. The expression of killer immunoglobulin like receptors (KIR) seems to be more variable [76-78].

Linker for activation of T cells (LAT), a membrane protein that plays an important role in T-cell activation, which appears early during T-cell development and is present on T- and NK-cells, among others, is expressed in the great majority of T- and NK-cell neoplasms [81]. CD70, the receptor for CD27, was also found to be expressed both on NK-cell lines and on NKTCL lymphoma cells [82].

Ki67 is also frequently positive and the percentage of Ki67⁺ cells has proven to be a prognostic factor in

extranodal NKTCL [83]. The Ki-67 protein (also known as MKI67) is a nuclear marker strictly associated with cell proliferation, which is present during all active phases of the cell cycle (G1, S, G2, and mitosis), but is absent from resting cells (G0) [84].

The fact that interactions between chemokines and chemokine receptors are involved in migration of lymphoma cells and tissue invasion have led to the investigation of chemokine receptor expression on NKTCL cells [69,70,74,75]. These studies revealed that NKTCL cells usually express CXCR3, whose main ligand is CXCL11 (IP9, IFN-gamma inducible protein type 9) [68-70]. In addition, ANKL cells are simultaneously positive for CXCR1 and CCR5, whose major ligands are CXCL1 (interleukin-8, IL-18) and the CCL3 (MIP-1alpha, macrophage inflammatory protein type 1 alpha), CCL4 (MIP-1beta) and CCL5 (RANTES, regulated on activation, normal T cell expressed and secreted) chemokines, respectively [74,75].

Primary nodal NKTCL have the same phenotypic and genotypic characteristics as extranodal NKTCL, at least for the markers that are frequently tested, most of them being described as being CD2⁺, sCD3⁻, cytCD3epsilon⁺, CD56⁺, EBV⁺ and as having the TCR genes in germ-line configuration; moreover, they also usually have a CD4⁻, CD5⁻, CD7⁻, cytotoxic molecules⁺ phenotype [48,49,52].

In overall, the immunophenotypic features of the neoplastic NK-cells from patients with NKTCL and ANKCL are different from those of normal peripheral blood NK-cells [85], reactive NK-cells from patients with acute and chronic NK-cell lymphocytosis associated with viral infections and tumors [86,87], and monoclonal CLPD-NK [88].

Chromosomal and genomic abnormalities

Cytogenetic analyses of the NK-cell neoplasms are difficult because of the scarcity of specimens, small-size samples, tissue necrosis and the presence of inflammatory cells. Despite these difficulties, several studies were performed to date [89-96], some of them using comparative genomic hybridization and loss of heterozygosity techniques. Currently, genetic abnormalities specific for NKTCL and ANKL have not yet been identified, although complex chromosomal aberrancies occur in a large fraction of cases, abnormalities of the chromosome 6 being the most frequent finding [89]. In overall, cytogenetic aberrancies are seen in up to 77% of cases and karyotypic abnormalities observed include pseudodiploidy (57%), hyperdiploidy (30%), and hypodiploidy (13%) [89]. Recurrent abnormal chromosomal losses are 6q16-q25, 11q23.1, 11q24-q25, 13q14.11 and 17p13.3, among others; chromosomal gains include 1q21-q44, 2q13-q14, 2q31.1-q32.2, 6p25-p11.1, 7q11.2-q34, 7q35-q36 and 17q21.1 [89-96]. A common deletion on 6q in the target area 6q21-25 was identified, affecting multiple genes that are

probably involved in oncogenesis and disease progression [90-96].

Concluding remarks

Mature NK cell neoplasms comprise a wide spectrum of entities, from cases with an indolent disease course (chronic NK-cell lymphocytosis) to cases with aggressive clinical behavior (NKTCL and ANKCL). Aggressive NK-cell neoplasms are EBV-related diseases with a particular geographic distribution, have a typical immunophenotype and complex karyotypic abnormalities, often affecting extranodal organs and tissues, invading and destroying the adjacent structures, causing hemophagocytosis and disseminating throughout the body. Due to their rarity, they are difficult to diagnose and to manage, and except for nasal NKTCL in early stages, they are refractory to the available therapies and have a very poor prognosis. Thus, multicentric registering studies and clinical trials are needed in order to better understand the disease biology and to develop new therapeutic agents.

Endnotes

^a The estimated incidence of NHL varies worldwide, with the highest rates being reported in the most economically developed regions of the world (e.g. Northern America, Australia/New Zealand, and Northern Europe) and the lowest rates in the least developed regions (e.g. South-Central and Eastern Asia, and the Caribbean). According to data provided by the Cancer Research, UK (<http://www.cancerresearchuk.org/>, accessed in 10 September 2011), the crude incidence rate in the UK in 2009 was 22 new NHL cases for every 100,000 males and 18 for every 100,000 females and within the countries of the European Union, the highest age standardized incidence rates for 2008 were estimated to be in Luxembourg for men (around 19 cases per 100,000) and Ireland for women (more than 13 cases per 100,000), while the lowest rates were found in Greece for both sexes (each around 3 cases per 100,000).

Abbreviations

ANKCL: Aggressive NK-cell leukemia; CCL3: C-C motif chemokine ligand type 3, also known as MIP-1alpha; CCL4: C-C motif chemokine ligand type 4, also known as MIP-1beta; CCL5: C-C motif chemokine ligand type 5, also known as RANTES; CCR5: C-C motif chemokine ligand type 5 (CD195); CLPD-NK: Chronic lymphoproliferative disorders of NK-cells; CXCL1: C-X-C motif chemokine ligand type 1, also known as IL-18; CXCL11: C-X-C motif chemokine ligand type 3, also known as IP9; CXCR1: C-X-C motif chemokine ligand receptor type 1 (CD181); CXCR3: C-X-C motif chemokine ligand receptor type 3 (CD183); EBNA: Epstein Barr virus nuclear antigens; EBV: Epstein-Barr virus; FasL: Fas ligand; ICD: International Classification of Diseases (now International Statistical Classification of Diseases and Related Health Problems); ICD-O: International Classification of Diseases for Oncology; IL-8: Interleukin-8 (CXCL1); IP9: IFN-gamma inducible protein type 9 (CXCL11); IPTCLP: International Peripheral T-cell Lymphoma Project; KIR: Killer immunoglobulin-like receptors; KLR: C-type lectin-like receptors; LAT: Linker for activation of T cells; LDH: Lactate dehydrogenase; LGL: Large Granular Lymphocytes; LMP: EBV-encoded latent membrane protein; MIP-1alpha: Macrophage inflammatory protein type 1 alpha (CCL3);

MIP-1beta: Macrophage inflammatory protein type 1 beta (CCL4); NHL: Non-Hodgkin's Lymphoma; NK: Natural killer; NK/TCL: NK/T cell lymphoma; PCR: Polymerase chain reaction; RANTES: Regulated on activation, normal T cell expressed and secreted (CCL5); TCR: T cell receptor; TIA-1: T-cell-restricted intracellular antigen; WHO: World Health Organization.

Competing interests

The author discloses any financial and non-financial competing interests that may influence the interpretation of data or the presentation of information in the manuscript.

Author's contributions

ML reviewed the literature on the subject, had write and approved the final manuscript.

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