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Nasal CD56 positive small round cell tumors

Differential diagnosis of hematological, neurogenic, and myogenic neoplasms

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Abstract CD56-positive nasal and nasal-type natural killer (NK)/T-cell lymphoma is now a well-defined disease entity. Rare cases of blastic NK-cell lymphoma positive for CD56 have been recently reported. However, CD56 expression is also identified in several types of non-hematopoietic small round cell tumors in which lymphoma is included as a differential consideration. Here, we present nine cases of CD56+ small round cell tumors of histological origin unrelated to nasal NK/T-cell lymphoma. Eight of the nine cases presented as solid tumors of the sinonasal region. Clinical, histological, ultrastructural, and immunohistochemical examination and gene analysis for T-cell receptor (TcR) and immunoglobulin heavy chain (IgH) genes and in situ hybridization (ISH) for Epstein-Barr virus (EBV) were performed. Two cases presented with features consistent with blastic NK-cell lymphoma or lymphoblastic lymphoma of NK-cell phenotype. These cases showed features of lymphoblastic lymphoma, phenotypes of sCD3–, cCD3+, CD45+, CD56+, TdT+, and human leukocyte antigen (HLA)-DR+, germline of IgH and TcR genes, and EBV negative reactivity. One case had myeloid/NK-precursor acute leukemia/lymphoma with a phenotype of CD13+, CD33+, CD34+, CD56+, and MPO–. Three cases were neurogenic, including one case of olfactory neuroblastoma and two of primitive neuroectodermal tumors (PNET). It was difficult to differentiate CD56+ PNET from blastic NK-cell lymphoma, especially when only paraffin-embedded sections were available. Myogenic markers, such as HHF35, α-sarcomeric actin, and desmin, were positive in three cases of rhabdomyosarcomas. Our findings suggest that as CD56 is used more routinely as a marker in immunohistochemical staining, the differential diagnosis of extranodal lymphohematological malignancies and small round cell tumors will become more complicated.

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Introduction

The neural cell adhesion molecule (NCAM), a member of the immunoglobulin (Ig) superfamily, mediates cell–cell adhesion interaction by homophilic (like to like) binding and is thought to be associated with the homing process of neoplastic cells to tissues that also express NCAM [4]. CD56 is a 140-kDa isoform of NCAM and is ubiquitously expressed on virtually all human natural killer (NK) cells and a subset of T lymphocytes [17, 18, 26]. Although CD16 and CD57 can also be used as markers for NK cells, CD56 is more often used as a reliable NK-associated marker. Well-defined CD56 positive NK-cell tumor entities have been described [11, 12, 13, 14]. However, CD56 expression has also been identified in a variety of unrelated hematopoietic neoplasms, including acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), and plasma cell myeloma [7, 19].

CD56 is not specific for hematopoietic cells. It is also frequently expressed in small round cell tumors of soft tissue, such as neuroblastoma, embryonal rhabdomyosarcoma, neuroendocrine tumors, and small cell carcinomas [3, 9, 20]. Because of similar morphological features and absence of cytoplasmic differentiation, accurate morphological diagnosis is often difficult. In addition to standard histological methods, supplementary techniques, such as histochemistry, immunohistochemistry, electron microscopy, and sometimes cyto- and molecular genetics are required to establish a correct diagnosis [5, 21].

Since CD56 is now routinely used as a marker for neoplasms suspected of NK-cell association, it is becoming clear that except for well-defined nasal NK/T cell lymphoma with angiocentric patterns, other CD56 positive diseases should be considered in the differential diagnosis. In this report, we present nine cases (most cases presented with solid tumors of nasal cavity or nasal si-

nus) of CD56+ small round cell tumors with histological origin unrelated to nasal NK/T-cell lymphoma. The clinical, histological, and immunohistochemical features are characterized, and the differential diagnosis is discussed.

Materials and methods

Nine cases of small round cell tumors with CD56 positivity presented in nasal areas other than nasal NK/T-cell lymphoma were reviewed and collected from the files of the First Department of Pathology–Hematology section of Fukuoka University. These cases were diagnosed between 1993 and 1999. The initial diagnoses could not determine the histological origin, and all cases were considered as malignant tumors of the small round cell group. In seven cases, both paraffin-sectioned and frozen materials were available. The materials for routine histological examination were fixed in buffered formalin and stained with hematoxylin and eosin. Clinical data were obtained from the physicians/medical records.

Immunohistochemical staining was carried out on frozen and/or paraffin sections. The antibodies T11 [CD2; Coulter Clone (CC); Hialeah, Fla.], Leu4 [sCD3; Becton Dickinson (BD); San Jose, Calif.], CD3e (cCD3; Dako; Glostrup, Denmark), OKT4 (CD4; Ortho; Raritan, N.J.), Leu-1 (CD5; BD), Leu9 (CD7; BD), OKT8 (CD8; Ortho), CALLA (CD10; BD), My7 (CD13; CC), My4 (CD14; CC), LeuM1 (CD15; BD), Leu11 (CD16; BD), B4 (CD19; CC), B1 (CD20; CC), interleukin (IL)2 (CD25; BD), Ki-1 (CD30; DAKO), Leu19 (CD56; BD), Leu7 (CD57; BD), βF1 [T-cell receptor (TcR)β; T-Cell Diagnostic; Cambridge, Mass.], δ1 (TcRδ; T-Cell Diagnostic), UCHL1 (CD45RO; Dako), leukocyte common antigen (LCA; CD45; Dako), L26 (CD20; Dako), My9 (CD33; CC), QBEnd-10 (CD34; Immunotech S.A.; France), MPO (Dako), TdT (Supertech; Bethesda, Md.), human leukocyte antigen (HLA)-DR (Dako), S-100 (Dako), neuron-specific enolase (NSE; Dako), grimelius, chromogranin A (Dako), α-sarcomeric actin (Dako), desmin (Dako), vimentin (Dako), HHF35 (Enzo Diagnostics Inc, Farmingdale, N.Y.), TiA-1 (CC), O-13 (CD99; Signet Laboratories, Inc.; Dedham, Mass.), latent membrane protein (LMP1; BD), early membrane antigen (EMA; Dako), cytokeratin AE1/AE3 (Dako), MIB1(Ki-67; Immunotech), EWS [c-19; Santa Cruz Biotechnology Inc. (SC); Santa Cruz, Calif.], EWS (N-18; SC), FLi-1 (c-19; SC), and WT-1 (c-19; SC) were used.

DNA from frozen (three cases) and paraffin-sectioned (five cases) materials was isolated in eight cases. Southern-blotting analysis (in three cases) and the polymerase chain reaction (PCR) method (in five cases) for the TcR gene β, γ, and immunoglobulin heavy chain (IgH) rearrangement were performed. Details of the examination methods have been described previously [23].

Epstein-Barr virus (EBV) RNA in situ hybridization (ISH) was carried out using paraffin sections in four cases to detect EBV. The details of the procedure were described previously [2]. Tissues from two cases were available for electron microscopic examination. The specimens, fixed in 2% glutaraldehyde and post-fixed in 1% osmium tetroxide, were processed routinely and examined with a JEM 100CX transmission electron microscope (Nihon Densi, Tokyo, Japan).

Results

The clinical features of all nine patients are summarized in Table 1. Four of the patients were males, and five were females. Their ages ranged from 1 year to 64 years. All but one case presented solid tumors in the nasal cavity, paranasal sinus, or adjacent areas (orbit and tongue). Case 2 presented with swelling of the lymph nodes of the neck. Case 1 has been previously reported [16] and also

Table 1 Clinical characteristics of nine cases of primitive small cell tumors. Duration is the follow-up time after diagnosis. *chem* chemotherapy; *radi* radiotherapy; *PBSCT* peripheral blood stem cell transplantation; *PR* partial remission; *CR* complete remission; *WND* without disease

Number	Age (years)	Gender	Site of involvement	Treatment and response	Duration	Status
1	47	Male	Tumor of nasal cavity and mediastinum with bone marrow involvement	Chem, resistant	8 months	Deceased
2	25	Male	Lymphadenopathy of neck progressed to systemic lymphadenopathy	Chem+PBSCT Relapsed at 9 month	10 months	Alive with disease
3	1	Female	Tumor of maxillary sinus with bone destruction, fever, peripheral blood, and bone marrow involvement	Chem, PR	5 months	Alive with disease
4	64	Female	Tumor of sphenoidal sinus	No information		
5	3	Female	Tumor of maxillary sinus with bone destruction	Chem+PBSCT, CR	11 months	Alive WND
6	46	Female	Tumor of tongue	Chem+radi, CR	10 months	Alive, WND
7	34	Male	Tumor of right nose, paranasal cavity and orbit with bone destruction	To information		
8	1	Female	Tumor of left nose with maxillary sinus involvement	Chem, CR	5 months	Alive WND
9	15	Male	Tumor of nose cavity, neck lymphadenopathy and bone marrow involvement	Chem+PBSCT, CR Relapsed at 13 months	15 months	Alive with disease

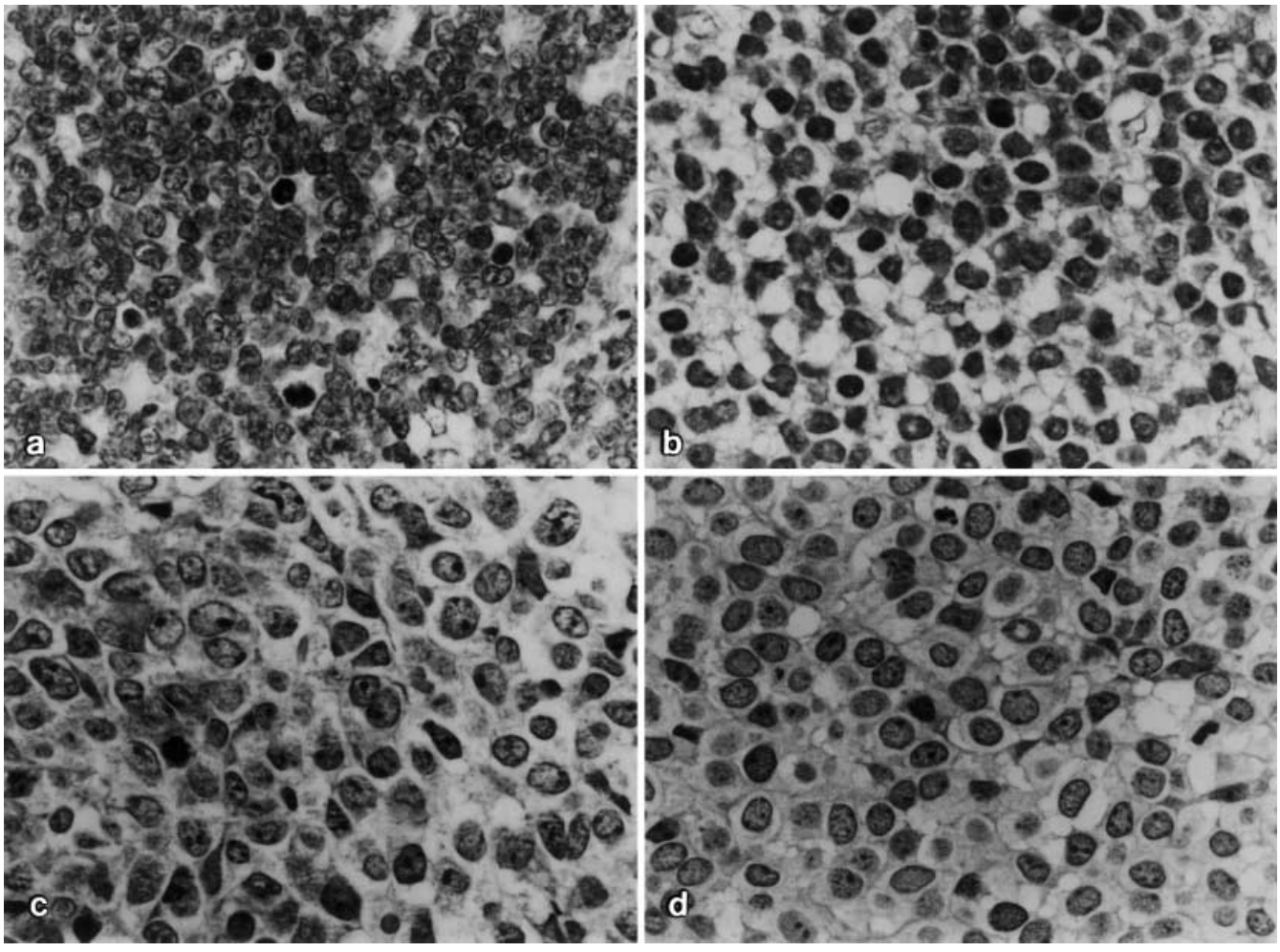

Fig. 1 Histological findings (hematoxylin and eosin staining). **a** Case 2, blastic natural killer (NK) cell lymphoma; **b** case 3, myeloid /NK precursor leukemia/lymphoma; **c** case 6, primitive neuroectodermal tumors; and **d** case 9, rhabdomyosarcoma

presented as a mediastinal tumor. Tumor cells were found in bone marrow in three cases (cases 1, 3, and 9). Blastic cells were detected in the peripheral blood in case 3. In all seven cases in which follow-up data were available, chemotherapy using a protocol for hematological malignancy was used. In case 5, therapy was later replaced with chemotherapy for sarcoma, followed by peripheral blood stem cell transplantation (PBSCT). One patient died at 8 months, and eight are still alive, two of the whom showed recurrence at 9 months and 13 months.

Histological features were consistent with those of small round cell tumors in all cases (Fig. 1). The initial pathologic diagnosis was malignant tumor of the small round cell group. Typically, diffuse or cohesive monomorphic proliferation of small blue cells was observed. Chromatin was finely distributed, nucleoli were usually small or indistinct, and cytoplasm was scanty. Nuclear mitosis was variable, with frequent mitosis encountered in case 1 and case 2. In case 4, a few sparse rosette-like features were detected and, in some areas, epithelial differentiation was noted. Case 7 showed nests of tumor cells separated by dense fibrous bands, giving irregular alveolar features in some areas. Most tumor cells had scanty cytoplasm, but a few cells had abundant eosinophilic cytoplasm, indicating myogenic differentiation.

The immunohistochemical results are shown in Table 2 and Fig. 2. In addition to a CD56 phenotype in all cases, phenotypes of blastic lymphoid cells were detected in case 1 and case 2. These two cases were cCD3+, CD5+, CD7+, CD45+, CD56+, TdT+, and HLA-DR+ but were negative for sCD3, CD19, CD20, CD45RO, TcRβ, TcRδ, and MPO. Case 2 was also positive for CD99. Case 3 showed an immature myeloid/NK-cell phenotype. This case was CD13+, CD33+, CD34+, and CD56+ but was negative for MPO, TdT, and lymphoid markers. Case 4 was positive by means of grimelius and chromogranin, but CD99, NSE, S-100, and lymphoid and myogenic markers were negative. Case 5 and case 6 were CD99+, NSE+, and CD56+, indicating a possible neuroectodermal origin. Case 7 and case 8 were positive for HHF35, α-SMA, and desmin, supporting a myogenic origin of tumor cells. Case 9 was only positive for HHF35 and desmin. A weakly positive reaction of EWS and FLI-1 was observed in case 6 and case 7.

Table 2 Immunohistochemical results of nine cases of primitive small cell tumors. *n* not done

	Antibody	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
CD2	T11	–	–	–	–	n	n	–	–	–
sCD3	Leu4	–	–	–	–	n	n	–	–	–
cCD3	CD3e	+	+	–	–	n	n	–	–	–
CD4	OKT4	–	–	–	–	n	n	n	–	–
CD5	Leu1	+	+	–	–	n	n	n	–	–
CD7	Leu9	+	+	–	–	n	n	n	–	–
CD8	OKT8	–	–	–	–	n	n	n	–	–
CD10	CALLA	–	–	–	–	n	n	n	–	–
CD13	My7	–	n	+	n	n	n	n	n	–
CD14	My4	–	n	n	n	n	n	n	n	–
CD15	LeuM1	–	n	n	n	n	n	n	n	–
CD16	Leu11	–	n	–	n	n	n	n	n	–
CD19	B4	–	–	–	–	n	n	–	–	–
CD20	B1	–	–	–	–	n	n	–	–	–
CD25	IL2	–	n	n	–	n	n	–	–	–
CD30	Ki–1	–	–	n	n	n	n	n	–	–
CD56	Leu19	+	+	+	+	+	+	+	+	+
CD57	Leu7	n	–	n	–	n	–	+	–	+
TCR B	BF1	–	–	n	n	n	n	–	n	–
TCR D	D1	–	–	n	n	n	n	–	n	–
CD45RO	UCHL1	–	–	–	–	–	–	–	–	–
CD45	CLA	+	+	–	–	–	–	–	–	–
CD20	L26	–	–	–	–	–	–	–	–	–
CD33	My9	–	n	+	n	n	n	n	n	n
CD34	QBEnd-10	–	–	+	–	–	–	–	–	–
	MPO	n	–	–	–	n	–	–	–	–
	TdT	+	+	–	–	n	–	–	–	–
	HLA-DR	+	+	–	n	n	n	n	+	n
	S-100	n	n	n	–	n	n	+	–	–
	NSE	n	–	–	–	+	+	n	+	–
	Grimelius	n	n	n	+	n	n	n	n	–
	Chromo[a]	n	–	n	+	n	–	n	n	–
	α-SMA	n	n	–	–	n	n	+	+	–
	Desmin	n	n	n	n	n	n	+	n	+
	Vimentin	n	n	n	n	n	n	+	+	+
	HHF35	n	–	n	–	n	n	+	+	+
	TiA-1	n	n	–	n	–	–	–	n	–
CD99	O-13	n	+	–	–	+	+	–	–	–
	EBV-LMP	–	–	n	n	n	n	–	–	–
	EMA	n	–	n	–	n	–	–	–	–
	CytoAE1[b]	–	–	n	–	n	–	–	–	–
	MIB1	+	+	n	–	n	+	n	+	–
	EWS(c-19)	n	–	–	–	n	+	+	–	–
	EWS(N-18)	n	–	–	–	n	+	+	–	–
	Fil-(c-19)	n	–	–	–	n	–	+	–	–
	WT-1(c-19)	n	–	–	–	n	–	–	–	–

[a] Chromogranin
[b] Cytokeratin AE1/AE3

Southern-blotting analysis in cases 1, 2, and 9, and PCR analysis in cases 3, 4, 6, 7, and 8 showed no clonal rearrangement of TcRβ, γ, and IgH. EBV was not detected using EBER1 ISH in the four cases (1, 2, 4, 8) examined. Electron microscopy showed a few electron-dense and membrane-bound dense granules in case 1. Tumor cells of case 6 showed numerous dense core granules in the cytoplasm. The results of histology, immunohistochemistry, gene analysis, EBV ISH, and probable diagnosis of all nine cases are summarized in Table 3.

Discussion

In the process of retrospective investigation of nasal NK/T-cell lymphoma, which is now a well-defined disease entity, we found a few cases of small round cell tumors in which it was difficult to make a specific diagnosis. Similar to nasal NK/T-cell lymphomas, these cases

Fig. 2 Immunohistochemical findings. **a** CD56+ of case 2; **b** TdT+ of case 2; **c** CD99+ of case 2; **d** LCA+ of case 1; **e** CD34+ of case 3; **f** CD13+ of case 3; **g** CD99+ of case 6; **h** NSE+ of case 6; **i** EWS(N-18)+ of case 6; **j** CD56+ of case 9; **k** HHF35+ of case 9; and **l** CD57+ of case 7 ▶

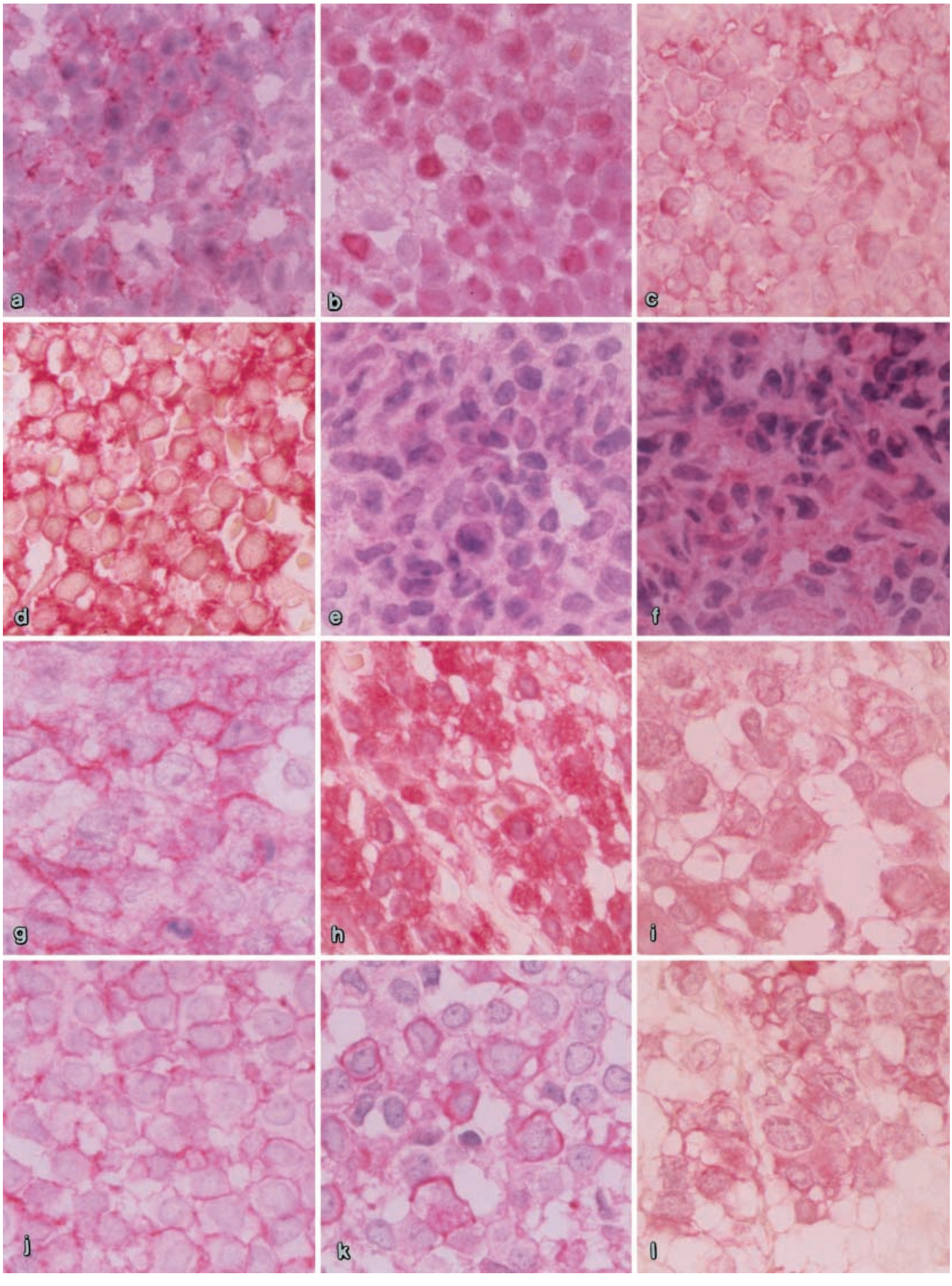
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Table 3 Summary of histology, immunohistochemistry, gene analysis, Epstein-Barr virus-in situ hybridization (EBV-ISH) and probable diagnosis. *N* not performed; *PNET* peripheral primitive neuroectodermal tumor; *NK* natural killer

Number	Histology	Immunohistochemistry	Gene analysis	EBV	Diagnosis
1	Monotonous, round nuclei, scanty cytoplasm, frequent mitosis	CD56+CD3+CD5+CD7+CD45+TdT+CD34–	Germline	–	Blastic NK-cell lymphoma
2	Bonotonous, round or oval nuclei, scanty cytoplasm frequent mitosis	CD56+CD3+CD5+CD7+CD45+TdT+	Germline		Blastic NK-cell lymphoma
3	Monotonous, round nuclei, fine chromatin, scanty cytoplasm, rare mitosis	CD56+CD13+CD33+CD34+ CD45-TdT-MPO–	N	N	Myeloid/NK precursor leukemia
4	Round or oval nuclei, pale cytoplasm, rare mitosis, rosettes and epithelial differentiation, dense core granules	CD56+grimelius+chromogranin+	Germline	N	Olfactory neuroblastoma
5	Monotonous, round nuclei, scanty cytoplasm, rare mitosis, crush artifact	CD56+NSE+O-13+CLA-TdT–	Germline	N	PNET
6	Cohesive, oval or angulated nuclei, scanty cytoplasm, occasional mitosis	CD56+NSE+O-13+CLA-TdT-EMA-cytokeratin–	Germline	–	PNET
7	Irregular nests of round or oval cells, scanty cytoplasm, occasional mitosis, a few cells with abundant cytoplasm	CD56+CD57+HHF35+α-SMA+desmin+	Germline	–	Rhabdomyosarcoma
8	Monotonous, round or oval nuclei, scanty cytoplasm, rare mitosis	CD56+HHF+α-SMA+	Germline	N	Rhabdomyosarcoma
9	Cohesive and monotonous, round nuclei, pale cytoplasm, rare mitosis	CD56+CD57+vimentin+HHF35+desmin+	Germline	N	Rhabdomyosarcoma

were also CD56 positive. Of the nine cases reported here, eight presented with tumors of the nose, nasal cavity, or surrounding areas, and their age varied widely from very young to old. Histologically, these cases manifested features of small blue cell tumors, i.e., tumor cells showed a diffuse or cohesive proliferation pattern with hyperchromatic nuclei, finely dispersed chromatin, and scanty cytoplasm. Specific diagnosis could not be done by means of histology alone. An extensive immunohistochemical investigation and/or genetic study in order to define the nature of tumor cells was encouraged.

Case 1 and case 2 showed features consistent with those of blastic NK-cell lymphoma, a newly recognized entity of NK-cell neoplasms. These cases manifested monomorphic proliferation of medium-sized lymphoid cells with fine chromatin, small or indistinct nucleoli, and scanty cytoplasm. Mitoses were frequently encountered in these cells. Immunohistochemically, tumor cells expressed CD45, cCD3, CD5, CD7, CD56, and TdT. However, the tumor cells were negative for sCD3 and CD45RO. Other markers of B cells and myelocytes were all negative. Gene analyses for IgH and TcR genes showed germline expression. ISH for EBER1 was nega-

tive. Therefore, an immature NK-cell origin of tumor cells was considered.

Lymphoblastic lymphomas can usually be classified as having a T- or B-cell origin. Recently, NK phenotype of lymphoblastic lymphoma or blastic NK-cell lymphoma has been described [6, 10, 12, 13, 15, 16, 22, 28]. Patients are predominantly middle-aged to elderly. Most reported cases presented with extranodal tumors, although few also manifested lymphadenopathy. Clinical course is usually progressive, while some tumors may respond to chemotherapy. Bone marrow is often involved. Morphologically, the tumor is characterized by a monomorphic proliferation of medium-sized cells with fine chromatin and scanty cytoplasm, resembling lymphoblasts. The cells are positive for CD56, a NK cell-associated marker. However, the cytoplasmic granules are usually scanty or absent. Furthermore, functional markers, such as granzyme B and TIA 1 are negative, reflecting the immature nature of tumor cells. Immunophenotypically, tumor cells are positive for CD45, CD43, CD56, and HLA-DR, but no consistency is found with respect to the expression of CD2, CD3, CD4, CD7, and CD34. Except for the report by DiGiuseppe et al. [6], most reported cases are TdT positive. The four cases in their study, associated with primary skin lesions, were TdT negative. EBV, detected using ISH for EBERs, was negative. Gene rearrangement studies for TcR and IgH were in the germline. Since the differentiation pathway of NK cells is not fully understood [29], tumor cells of blastic NK-cell lymphoma may vary from bipotential T/NK progenitors to committed NK-cell precursors [10].

Recently, Suzuki et al. [30] described a new hematolymphoid disease entity as myeloid/NK cell precursor acute leukemia. This type of leukemia is characterized by extramedullary involvement of peripheral lymph nodes and mediastinum at initial presentation, but the liver and spleen are usually spared from tumor involvement. Myeloid and NK-cell precursor phenotypes were detected expressing CD7, CD33, CD34, CD56, and frequently HLA-DR. MPO and other T- and B-cell markers and TdT were negative. The TcR β and γ genes and Ig heavy gene were expressed in the germline. Our present case 3 showed a similar clinical presentation with fever, blast cells in peripheral blood and bone marrow, and solid tumor of the maxillary sinus. Histological examination of the maxillary tumor showed a monomorphic proliferation of small blue cells with fine chromatin, small or indistinct nucleoli, and scanty cytoplasm. Mitosis was rarely found in these cells. Immunohistochemically, the phenotype was also similar. The tumor cells were positive for CD13, CD33, CD34, and CD56, although CD7 and HLA-DR were negative. It was determined that case 3 had myeloid/NK-cell precursor acute leukemia.

Recently, Bjornson et al. [1] found that neural stem cells could be induced to differentiate into hematopoietic cells. It is implied that some immature neurogenic malignancies may manifest features of myelogenic neoplasms, and the differentiation between some neurogenic and myelogenic malignancies may be very difficult. Peripheral primitive neuroectodermal tumors (PNET) are the prototype of small round cell tumors [21]. Morphologically, PNET is composed of monotonous small round cells with scanty cytoplasm. True rosettes and Homer Wright rosettes represent histological evidence of neural differentiation. Immunohistochemical staining usually shows a positive reaction for CD99 and NSE and a variable staining pattern for other neural markers. Cytogenetic abnormalities include t(11,22)(q24;q12). Translocation results in the fusion of the EWS gene in 22q12 with the FLI-1 gene in 11q24. CD56 expression has been reported in some cases of PNET [3, 9, 20]. These cases of CD56+ PNET can pose a differential diagnosis problem with CD56+ immature hematolymphoid neoplasms, such as blastic NK-cell lymphoma, especially when only paraffin-embedded tissues are used for diagnosis. Histologically, rosette features may not be obvious in PNET. However, even the presence of Homer Wright rosettes in blastic NK-cell lymphoma has been reported [15]. Immunohistochemically, the reliable hematolymphoid marker, LCA, may be negative in lymphoblastic lymphoma in paraffin sections [8, 24]. The routinely applied PNET marker, MIC2 protein (CD99), is frequently expressed in lymphoblastic lymphoma and acute lymphocytic leukemia (ALL) [25]. Our single case of blastic NK-cell lymphoma was also MIC2 (detected by antibody O13) positive. We were confronted with such difficulties in case 5 and case 6. Frozen materials were not available in these two cases. Rosettes were not observed histologically. Immunohistochemically, tumor cells were immunoreactive to CD56, CD99, and NSE. The strong positive reaction for NSE favored a neurogenic origin of the tumor cells [21]. One of these two cases showed a weakly positive reaction for EWS and FLI-1. Paraffin sections of our two cases of blastic NK-cell lymphoma were TdT positive. It seems that TdT positivity favors blastic NK-cell lymphoma rather than PNET.

Expression of CD56 is frequently observed in rhabdomyosarcomas. Normal skeletal muscle cells are negative, indicating that NCAM expression may be induced after malignant transformation of certain NCAM target cells [3]. Of the three cases reported here with suspected rhabdomyosarcoma, only one showed myogenic differentiation in a few tumor cells upon histological examination. Immunohistological staining using myogenic markers is very helpful in poorly differentiated cases. The present case 9 is especially interesting. Clinically, the patient manifested multiple pathological fractures, a solid tumor in the nasal cavity, and cervical lymphadenopathy. Infiltration of small round tumor cells were detected in the bone marrow. A lymphohematological neoplasm was clinically suspected. Histological examination showed features of a typical small blue cell tumor without cytoplasmic differentiation. The initial immunohistochemical studies showed only CD56 positivity, but all other lymphohematological markers, neurogenic markers, and myogenic markers (myoglobin and myosin) were negative. Southern blotting for the TcR gene and the Ig gene showed expression in the germline. Further immunohis-

tochemical staining indicated that the tumor cells were positive for HHF35 and desmin. False-positive reaction of muscle-specific actins in non-Hodgkin's lymphomas has been reported [27]. This case was most likely a poorly differentiated rhabdomyosarcoma. The patient was treated with a course of CHOP (cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone) chemotherapy and PBSCT, which induced a complete remission, although relapse was noted 13 months after therapy. At relapse, some spindle cells with myogenic differentiation were noted.

In recent years, our understanding of NK-cell neoplasms have undergone a dramatic expansion. At present, both mature and immature forms of these tumors have been well characterized. The mature form of NK-cell neoplasms usually exhibits pleomorphic cytology, cytoplasmic azurophilic granules, and positive reaction to cytotoxic markers, such as TIA-1, and possible EBV association. In contrast, immature NK-cell malignancies often manifest a monomorphic cytology, few cytoplasmic granules, no functional cytotoxic reaction, and are negative for EBV. These features may cause diagnostic problems for a given immature NK-cell neoplasm to be differentiated from other CD56+ hematological neoplasms and CD56+ small round cell tumors of soft tissues. This is especially true when limited biopsy material is available, which may make extensive immunohistochemical, cytogenetic, and molecular genetic investigation impossible.

In conclusion, we reported here nine cases of CD56 positive small round cell tumors of different histological origin. We found that as CD56 antigen becomes a widely used marker in the diagnosis of malignancies suspected of NK-cell association, differentiation between immature NK-cell neoplasms and small round cell tumors of soft tissue will become much more complicated.

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