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BRIEF COMMUNICATION

Partial trisomy of chromosome 13 as a single cytogenetic abnormality in an Italian case of nasal NK/T lymphoma

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Extranodal NK/T lymphoma, nasal type, is an uncommon neoplasm that occurs with a higher prevalence among Asian populations and Native American populations of Central and Southern America. In Western countries, this tumor is extremely rare, accounting for less than 1.5% of all non-Hodgkin lymphomas. Cytogenetic analyses have been performed only in a limited number of cases, mainly because of technical problems related to extensive necrosis and the scarcity of clinical samples, and these have shown complex karyotypes with no specific chromosomal translocations. Here, we report the cytogenetic characterization of a clinically aggressive nasal NK/T-cell lymphoma occurring in a 40-year-old Italian male patient, in which the sole chromosome abnormality was a partial trisomy of chromosome 13.

Keywords Extranodal NK/T lymphoma, nasal type, FISH, spectral karyotyping

Extranodal NK/T lymphoma, nasal type, is one of the two mature NK-cells-derived neoplasms reported in the most recent World Health Organization (WHO) classification of lymphoid tissues. Although this lymphoma is more prevalent in Asia and Central and Southern America, some rare cases have also been reported in Europe and North America. The typical site of origin is the nasal cavity and upper aerodigestive tract, which is the reason why this lymphoma has been designated as "nasal type." Extranasal sites of origin include several extranodal organs, whereas solitary nodal involvement in the absence of other localizations has been anecdotally reported (1).

Extranodal NK/T lymphoma, nasal type, is an Epstein-Barr virus (EBV)related neoplasmregardless of the patient's ethnic origin. The virus appears to play an important etiological role in lymphomagenesis, and its detection in neoplastic cells is a desirable criterion for a correct diagnosis (2,3).

Conventional and molecular cytogenetic analyses of this lymphoma have only been performed in a limited number of cases, mainly because of technical problems related to extensive necrosis and the scarcity of clinical samples. No specific pattern of chromosomal abnormalities has been identified yet, although the most common changes are deletion of chromosomes 6q, 8p, 11q, 12q, and 13q, and gains of chromosomes 2q, 15q, 17q, and 22q. No specific chromosomal translocation has been reported (4–9).

Here, we report the cytogenetic characterization of a clinically aggressive nasal NK/T-cell lymphoma in a 40-year-old Italian male patient.

Case report and histopathological examination

A 40-year-old male patient was admitted to the otorhinolaryngology department of another institution because he had nasal polyposis and chronic rhinosinusitis, for which he underwent functional nasal surgery and ablation of inferior turbinates. One year later, after a trip to the Sahara Desert, he was referred to the otolaryngology department of our hospital, with fever, persistent rhinorrhoea with crostous lesions of nasal mucosa, and enlargement of cervical lymph nodes.

The microbiological examination of nasal samples was positive for *Streptococcus viridians* and *Enterococcus faecalis* group D, but serial hemocultures were negative.

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Anti-EBV IgM and anti-Cytomegalovirus antibodies were negative, as were anti-*Treponema pallidum* and anti-*Toxoplasma gondi* antibodies. In addition, *Plasmodium falciparum* research was negative. An antibiotic therapy was started.

The ultrasonographic examination of the neck demonstrated multiple bilateral adenopathies. The fine needle aspiration of one lymph node showed atypical lymphoid cells suspect for lymphoproliferative disease. In this setting, the patient underwent surgical excision of a cervical lymph node and multiple biopsies of the nasal cavity, rhinopharynx, and paranasal sinuses.

At routine histopathological examination, the mucosal samples were largely necrotic. In one rhinopharyngeal biopsy, a diffuse proliferation of small and medium-sized atypical lymphoid cells was observed, focally invading the wall of blood vessels in an angiocentric fashion. In the lymph node sections, the normal architecture was completely effaced by a lymphomatous proliferation with the same features as described in the rhinopharynx, showing focal areas of necrosis. The immunophenotype of lymphoma cells was CD2+, CD3ε+, CD56−/+, Granzyme B+, TIA−1+, perforin+ and CD20−, CD4−, CD8−, CD10−, CD30−, CD57−, MUM1−. In situ hybridization for eeEBV-RNA (EBER) was positive. A diagnosis of extranodal NK/T lymphoma, nasal type, was formulated (Figure 1).

Staging procedures with a CT scan, MRI, and PET scan revealed the presence of pathological tissue involving the nasal mucosa and mascellar sinuses bilaterally, the perirhinopharyngeal soft tissues and the left orbital cavity. Pathological enlargement of lymph nodes at all cervical stations was also documented. A bone marrow biopsy was positive for lymphoma localization.

The patient underwent two cycles of chemotherapy with the CHOP (cyclophosphamide, doxorubicin, vincristin, prednisone) scheme, but no response was observed and he died 45 days after diagnosis with pulmonary progression of the disease and septic shock. A post-mortem examination was not performed.

Cytogenetic analysis

A fresh tumor sample of the cervical lymph node was minced into small pieces, incubated, and processed according to the method described by Tibiletti et al. (10). Conventional chromosome analysis was performed on direct preparations that were incubated for 24 hours. Slides were QFQ-banded (Q-bands by fluorescence using quinacrine6) and analyzed according the recommendations of the ISCN 2009 (11). The cytogenetic study revealed the presence of a marker chromosome in all the analyzed metaphases, and the neoplastic karyotype was 47,XY,+mar. Fluorescence in situ hybridization (FISH) was performed, to better define the marker chromosome, with commercially available probes for T-cell receptor alpha/delta (*TCRAD* on 14q11), beta (*TCRB* on 7q34), and gamma (*TCRG* on 7p14) (Dako Italia S.p.A., Milano, Italy), again according to the procedure described by Tibiletti et al. (10). The marker chromosome was negative for all these probes. As expected, based on the histologic diagnosis, no T-cell receptor rearrangement was detected. Spectral karyotyping FISH (SKY-FISH) was performed as previously described by Calabrese et al. (12), and the analysis defined the marker chromosome as a derivative of chromosome 13 (Figure 2). FISH performed with probes RB1 and DLEU1 for

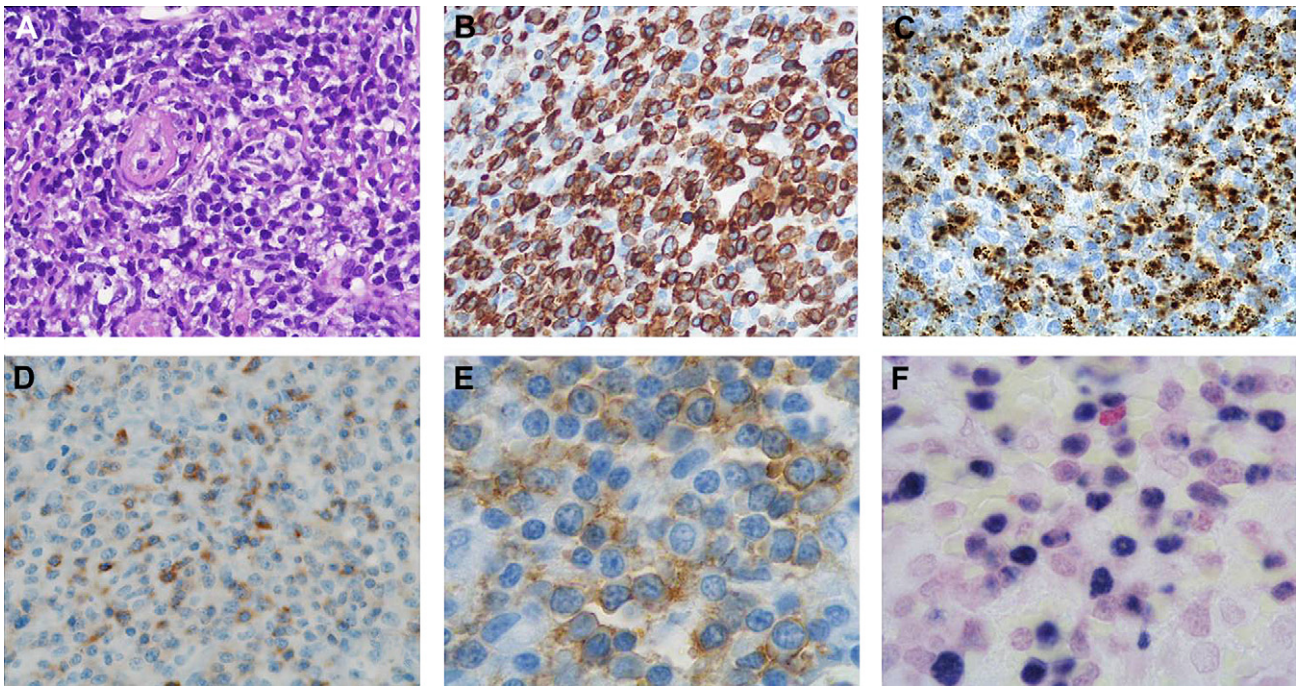

Figure 1 Histopathological features of the reported nasal NK/T lymphoma. In non-necrotic areas, the tumor was composed of a diffuse proliferation of small and medium-sized atypical lymphoid cells, focally invading the wall of blood vessels in an angiocentric fashion (A) (H & E, original magnification ×400). At immunohistochemical analysis, lymphoma cells were strongly CD3ε-positive (B) and granzyme B-positive (C) but faintly immunoreactive for CD2 (D) and CD56 (E). In situ hybridization demonstrated that EBV-RNA (EBER) was present in the neoplastic nuclei (F).

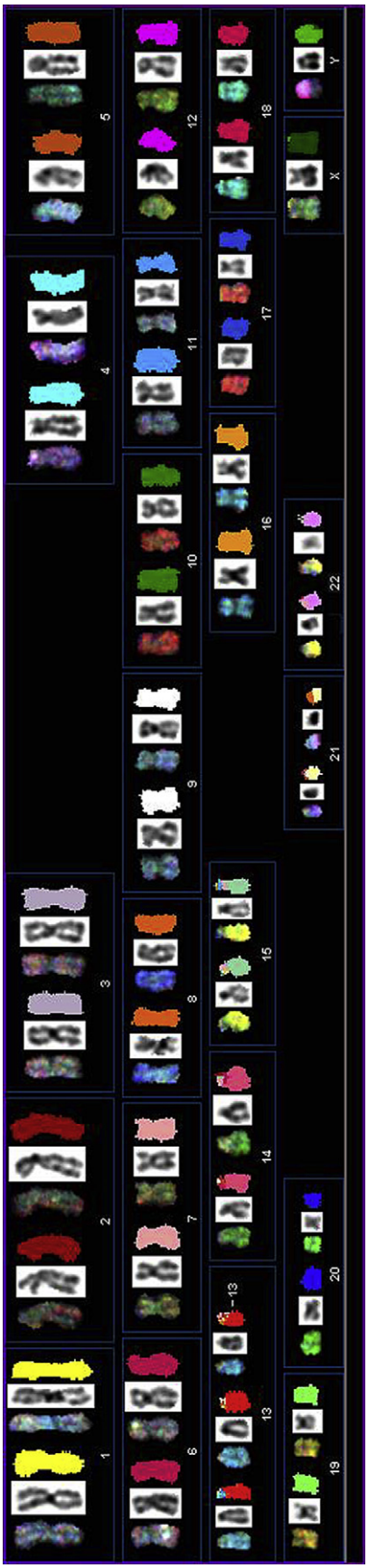

Figure 2 SKY-FISH. The marker chromosome was identified as a derivative of chromosome 13.

the 13q14 region and with probe D13S1160 for the 13qter region (all three probes from Abbott Molecular Europe, Wiesbaden, Germany) revealed a partial trisomy of chromosome 13. Specifically, the marker chromosome was negative for the two 13q14 probes and was positive for the 13qter probe. The final karyotype of the nasal NK/T-cell lymphoma was defined as: 47,XY,+mar.ish der(13)(*WCP13*+,*TCRG*−,*TCRB*−,*Rb*−,*DLEU1*−,*D13S1160*+,*TCRAD*−).

Discussion

We conducted a detailed cytogenetic analysis of a case of extranodal NK/T lymphoma that was well characterized from a morphological and clinical point of view. Cytogenetic investigation revealed a partial trisomy of chromosome 13 as the sole chromosome abnormality in the neoplastic cells. To our knowledge, this is the first report of a partial trisomy of chromosome 13 as a single cytogenetic aberration in any type of EBV-positive NK-cell leukemia or lymphoma since the establishment of standardized diagnostic criteria for NK-cell neoplasms by WHO. The most common cytogenetic aberration reported in extranodal nasal NK/T-cell lymphoma is loss of 6q. Conventional cytogenetic analysis, FISH, and spectral karyotyping have established 6q deletions, particularly deletions of 6q21, 6q23, and 6q24-27, as common recurrent aberrations in this neoplasm (5). Additional recurrent chromosome abnormalities include loss of 11q and 13q, loss of 17p, gain of the X chromosome, and gain of 20q and 13q (4–6,8,9). All these aberrations are consistently present in complex karyotypes with multiple numeric and structural abnormalities. A review of the literature revealed only one extranodal nasal NK/T-cell lymphoma showing an isochromosome 7q10 as a single chromosome abnormality (13) and a case of nasal NK/T-cell lymphoma with a constitutional 11q terminal deletion and an acquired t(1;14) of the bone marrow specimen (14). The partial trisomy of chromosome 13 is the sole chromosome abnormality in the otherwise diploid karyotype of this case; therefore, it may be speculated that it is related to the early pathogenesis of the disease. FISH analysis demonstrated that the trisomic region did not encompass the *RB1* and *DLEU1* regions. This observation may indicate that the partial trisomy of chromosome 13 could have originated by two hits involving the deletion of the *RB1* and *DLEU1* regions and the subsequent malsegregation of normal chromosome 13, or vice versa. Gains of chromosome 13q in extranodal nasal NK/T-cell lymphoma have been reported by other authors as a part of complex karyotypes (5,6,8). Interestingly, the described 13q gains mapped to bands 13q21 and 13q31-33, which is the same region involved in the partial trisomy of our case. These bands contain several unidentified proto-oncogenes, including the G-protein-coupled receptor 18 (4,15).

In conclusion, we have reported the case of a clinically aggressive extranodal NK/T lymphoma, nasal type, which occurred in an Italian patient, with a unique pattern of cytogenetic alterations. The correlation between the partial trisomy of chromosome 13 and the early nodal involvement, as well as the rapidly fatal course of this lymphoma, remains to be established.

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