

## Therapy-related acute leukemia associated with involvement of 11q23 after high grade non-Hodgkin lymphoma

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**Therapy-related acute myeloid leukemias with balanced translocations affecting the 11q23 chromosome region are one of the most serious complications of treatments with topoisomerase II inhibitor drugs as epipodophyllotoxins and anthracyclines. 1, 2-5 These cases are usually associated with short interval time from previous chemotherapies, absence of myeloid dysplastic phase, hyperleukocytosis and young age. We and others have recently identified and cloned the ALL1 gene at 11q23 band (also named MLL, HRX, Hrxt) which is consistently altered in t-AML following therapies with topo II targeting drugs. 1 However, there are few reports of cases of t-AML, clinically and biologically similar to the subtype of leukemias secondary to exposure to topo II inhibitors drugs but without the involvement of the ALL1 gene. These observations suggest that genes other than ALL1 which are etiopathogenetically relevant for hematological neoplasias are located in this cytogenetic region.**

A 27-year-old man was admitted to our institution in June 1994 with a 4-week history of fever, anorexia and weight loss. Chest X-ray and CT scan showed a mediastinal mass with enlargement. A bone marrow (BM) aspirate and biopsy revealed normocellular BM. The diagnosis of high-grade B-cell lymphoblastic NHL with sclerosis was made on a needle biopsy of the mediastinal mass. No cytogenetic analysis was done on the BM at diagnosis. The clinical stage was defined as IA *bulky*.

From September 1994 to January 1995 the patient received 11 courses of the MACOP-B chemotherapy with cytosine arabinoside, vincristine, adriablastine, methotrexate and etoposide, achieving only partial remission due to the persistence of 20% of the initial mediastinal mass.<sup>3,4</sup> Local radiotherapy (RT) (3600 cGy/fac, with inverted fields) was administered from March to April 1995. One week after the end of RT, an hemochromocytometric analysis revealed  $19 \times 10^9/L$  WBC with 98% of blasts with monocytic features. At this time the BM biopsy showed a total substitution by leukemic blasts. On the basis of standard morphological, immunological and cytochemical criteria a diagnosis was made of acute myeloid leukemia, FAB M4. The karyotype was 46 XX, t(7;11)(p21;q23), t(10;X)(p14;q24). The ICE protocol was administered as treatment of AML without achieving a CR.<sup>2</sup> The patient died from infective complication in June 1995.

An ALL1 germline genomic configuration was detected by Southern blot analysis of DNA from both the mediastinal mass at the time of diagnosis of NHL and from BM leukemic blasts at the onset of AML. To this purpose DNA was digested to completion with *Bam* HI and *Hind* III endonucleases and hybridized with the B859 probe, which is a cDNA insert containing the ALL1 exon 5-11 sequences.

Our case report allows us to draw some possible etiopathogenetic suggestions on t-AML leukemogenesis. Firstly, the observation from the literature that none of the rare cases of NHL with 11q23 developed a t-AML rule out the hypothesis that t-AML represents an evolution of the natural history of the disease.<sup>7,8</sup> It is well known in fact that t-AML after NHL is a serious complication of treatments including topo II inhibitors drugs usually with consistent involvement of the ALL1 gene at 11q23.<sup>3</sup> Moreover, the identification within the ALL1 breakpoint cluster region of DNA structures involved in the topo II machinery, such as high-affinity scaffold attachment regions and topoisomerase II binding sites, has provided a strong pathogenetic linkage in this leukemic subset between chemotherapeutic agents and targeting gene.<sup>6</sup>

However, the observation that the ALL1 gene is not always altered in cases with clinical, biological and cytogenetic features similar to those of ALL1+ t-AML suggests that in the 11q23 cytogenetic band gene(s) other than ALL1 could exist that are involved in the pathogenesis of t-AML. In this respect, it is interesting to note at least two other genes implicated in hematological malignancies which have been identified within this cytogenetic region: namely, the p54/RCK gene found altered in two B cell malignant lymphomas with t(11;14)(q23;q32) cytogenetic translocation, and the PLZF gene coding a ZF protein which is fused to the RARA in acute promyelocytic leukemia with t(11;17)(q23;q21) abnormality.<sup>6-10</sup> In conclusion, the present case provides further evidence of the need to search for other gene(s) located in this region which could be involved in the pathogenetic mechanism leading to t-AML after exposure to chemotherapeutic treatments.

### Funding

*This work was supported by Associazione Italiana per la Ricerca sul Cancro (A.I.R.C.), by Italian C.N.R "A.C.R.O." no. 94.01222 and by 95.2206 C.N.R. target projects.*

### Key words

*Non-Hodgkin's lymphoma, 11q23, acute leukemia*

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### ***Achromobacter xylosoxidans* bacteremia in patients with hematologic malignancies**

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**We report nine cases of *Achromobacter xylosoxidans* bacteremia diagnosed in patients with hematologic malignancies. There was not an obvious epidemiologic link between cases and the organism was not isolated from any source. Outcome was cure in all nine cases. In our experience, catheter removal is generally required for eradication of *A. xylosoxidans*.**

*Achromobacter xylosoxidans* is a non-fermenting gram-negative rod widely distributed in the environment, like hospital fluids, from which outbreaks of nosocomial infections may occur.<sup>1-3</sup> About 90 cases of *A. xylo-*

*soxidans* bacteremia have been reported, twenty-one out of these in patients with hematologic malignancies, though eleven occurred as an infectious outbreak in a hematology ward.<sup>4-6</sup>

Between January 1993 and April 1997, the data of 8 patients from the department of hematology who suffered *A. xylosoxidans* bacteremia were recorded. One patient had two infections separated by 8 months and has been included twice.

Tables 1 and 2 show the patients characteristics of the series. All cases of bacteremia were not related with each other by time or space and *A. xylosoxidans* was not isolated in hospital environment nor any other source than blood cultures. Patients received empiric broad spectrum antibiotics and they were changed if resistance was demonstrated.

None of the patients developed septic complications or deep-seated infections, suggesting that *A. xylosoxidans* is a non-virulent organism even in highly compromised hosts. Six isolates were sensitive to ampicillin and eight to amoxicillin-clavulanate. Six cases were resistant to all first and second generation cephalosporins and two to ceftazidime. All species were resistant to gentamicin and tobramycin and two cases were sensitive to amikacin. On the other hand, susceptibility to the fluorquinolones, ticarcillin, piperacillin and carbapenems was universal. One case was resistant to co-trimoxazole.

*A. xylosoxidans* is an infrequent human pathogen, but various different types of infections have been reported, including primary bacteremias and deep-seated infections in normal individuals or patients with multiple underlying conditions.<sup>7,8</sup>

Although *A. xylosoxidans* bacteremia is uncommon, we have observed nine episodes in the last four years. During this period, 541 adult patients received intensive chemotherapy and 40 cases of non-fermenting

**Table 1. Patient characteristics. I.**

Cases	Sex/age	Underlying disease	Recent BMT (days)	Severe neutropenia	In-patient
1	M/22	NHL	APBSCT (+3)	yes	yes
2	M/40	CML	APBSCT (+3)	yes	yes
3	M/40	HD	ABMT (+2)	yes	yes
4	M/27	ALL	ABMT (+3)	yes	yes
5	F/33	ALL	none*	yes	no
6	M/46	AML+GVHD	BMT (49 months)	no	no
7	M/46	AML+GVHD	BMT (57 months)	no	no
8	M/59	MM	APBSCT (+3)	yes	yes
9	M/43	HD	APBSCT (+2)	yes	yes

\*Consolidation chemotherapy. NHL: non-Hodgkin's lymphoma; CML: chronic myelogenous leukemia; HD: Hodgkin disease; ALL: acute lymphoid leukemia; AML: acute myelogenous leukemia; GVHD: graft-versus-host disease; MM: multiple myeloma; APBSCT: autologous bone marrow transplantation; BMT: allogeneic bone marrow transplantation.