Absence of p53 mutation in 15 cases of myeloid malignancies with structural rearrangements of 3q

Sir,

Structural abnormalities affecting the long arm of chromosome 3, mostly presenting as inv (3)(q2;1q26) or t(3;3)(q21;q26), have been reported in 2% of acute myelogenous leukemias (AML). These lesions have been described in all FAB subtypes except M3. Furthermore, they can be encountered in some cases of myelodysplastic syndromes (MDS) and in the blastic crisis of chronic myeloid leukemia (CML-BC). The response that patients with these lesions have to conventional antileukemic therapy is uniformly poor.[1-8]

p53 abnormalities are the most common molecular lesions found in human cancer. p53 inactivation is associated with resistance to chemotherapy and short survival in hematologic malignancies. In AML, p53 is inactivated in 5-15% of cases. In most cases, lesions at 17p are detected at the cytogenetic level.[9]

In the present study, we analyzed 15 cases of myeloid malignancies with rearrangements of 3q by PCR-SSCP in order to ascertain whether or not p53 mutations contribute to the bad outcome observed in these disorders.

Table 1. Clinical data and cytogenetic findings.

Pts.	Age	Sex	Diagnosis	Karyotype	Outcome
1	36	M	AML	45,XY,inv (3)(q21; q26), -7	Dead refractory disease
2	NI	F	AML	45,XX,inv (3)(q2; 1q26) /46,XX	NI
3	29	F	AML	45;XX,inv (3)(q21; q26), -7	Dead refractory disease
4	56	F	AML	45,XX,inv (3)(q21; q26), -7	Dead relapse 12 months after TMO
5	NI	F	AML	45,XX,inv (3)(q21; q26),-7	NI
6	NI	M	MDS	46,XY,inv (3)(q21; q26), del(5)(q21q23)	NI
7	24	F	AML	45,XX,inv (3)(q21; q26), -7	NI
8	26	F	AML	45,XX,inv (3)(q21; q26), -7	NI
9	NI	M	AML	45,XX,inv (3)(q21; q26), -7,12p+	NI
10	36	M	AML	46,XY,t (3;3)(q21; q26) / 46,XY	Dead refractory disease
11	65	M	CMML	45,XY,t (3;21)(q26; q22), -7	Dead progressive disease
12	42	F	BC-CML	46,XX,t (9;22)(q34q11), t (3;21)(q26q22)	Dead progressive disease
13	NI	M	MDS	45,XY,-7,-10,+der(10),t(3;10)(q21; q26)	NI
14	19	M	AML	46,XY, t (3;5)(q25; q34) / 46,XY	NI
15	NI	M	MDS	46,XY,del (3)(q13q25) /46,XY	NI

NI: no information available.

Patients were selected from all the samples submitted to the Hospital Sant Pau for cytogenetic study from 1993 to 1997. The selection criterion was the detection of an abnormality affecting chromosome 3 in patients with myeloid malignancies.

PCR-SSCP and DNA sequencing reactions were performed as described elsewhere.[10]

The clinical data and the karyotype are shown in Table 1. Ten patients had structural rearrangements at 3q21q26 and five had other cytogenetic lesions affecting 3q. There was an associated monosomy 7 in 9 cases. Clinical information available for 6 patients showed a fatal course in all the cases. We found no abnormal conformers in exons 5 to 9 by SSCP, indicating that there were no pathogenic mutations.

We have reviewed the literature and in 153 cases with myeloid malignancies and 3q rearrangements including those of this series,[1-8] there were only 5 cases with associated cytogenetic involvement of the short arm of chromosome 17. Fonatsch *et al.*[3] found 2 cases with t(7;17) and t(17;21) and Secker-Walker *et al*.[1] reported 2 cases with monosomy 17 and one case with trisomy 17.

Despite the small number of cases examined in this study, it could be concluded that unknown gene alterations in chromosomes 7 and 3 are probably responsible for disease pathogenesis and poor prognosis in these patients.

Luz Muñoz, Camino Estivill, Anna Aventín, Conxa Boqué, Olga López, Josep F. Nomdedéu*

*Departament d'Hematologia de l'Hospital de Sant Pau and *Institut Català Oncologia, Barcelona, Spain*

Key words

p53 mutation, 3q rearrangement.

Acknowledgemnts

This study was supported by a grant from the FIS (97/1118)

Correspondence

Josep F. Nomdedéu, M.D., Hospital de Sant Pau, 08025 Barcelona. Spain. Fax: international + 34-93-2919192 – E-mail: jfnomde@santpau.es

References

1. Secker-Walker LM, Metha A, Bain B. Abnormalities of 3q21 and 3q26 in myeloid malignancy: a United Kindom Cancer Cytogenetic Group study. Br J Haematol 1995; 91:490-501.
2. Horsman DE, Gascoyne RD, Barnett MJ. Acute leukemia with structural rearrangements of chromosome 3. Leuk Lymphoma 1995; 16:369-77.
3. Fonatsch C, Gudat H, Lengfeldder E, et al. Correlation of cytogenetic findings with clinical features in 18 patients with inv(3)(q21;q26) or t(3;)(q21;q26). Leukemia 1994; 8:1318-26.
4. Grigg AP, Gascoyne D, Phillips GL, Horsman E. Clinical, haematological and cytogenetic features in 24 patients with structural rearrangements of the Q arm

of chromosome 3. Br J Haematol 1992; 83:158-65.
5. Shi G, Weh HJ, Dührsen U, Zeller W, Hossfeld DK. Chromosomal abnormality inv(3)(q21q26) associated with multilineage hematopoietic progenitor cells in hematopoietic malignancies. Cancer Genet Cytogenet 1997; 96:58-63.
6. Levy ER, Parganas E, Morishita K, et al. DNA rearrangements proximal to the EVI1 locus associated with the 3q21q26 syndrome. Blood 1994; 83:1348-54.
7. Sacchi N, Nisson PE, Watkins PC, Faustinella F, Wijsman J, Hagemeijer A. AML1 fusion transcripts in t(3;21) leukemia: evidence for molecular heterogeneity and usage of splicing sites frequently involved in the generation of normal AML1 transcripts. Genes Chrom Cancer 1994; 11:226-36.
8. Nucifora G, Birn DJ, Espinosa III R, et al. Involvement of the AML1 gene in the t(3;21) in therapy-related leukemia and in chronic myeloid leukemia in blast crisis. Blood 1993; 81:2728-34.
9. Fenaux P, Jonveaux P, Quiquandon I, et al. p53 gene mutations in acute myeloid leukemia with 17p monosomy. Blood 1991; 78:1652-7.
10. Nomdedéu JF, Lete I, Baiget M, et al. Mutational analysis of p53 in 16 cases of acute lymphoblastic leukemia and Burkitt's lymphoma. Haematologica 1997; 82:550-4.

Invasive cerebral aspergillosis in a patient with aplastic anemia. Response to liposomal amphotericin and surgery

Sir,

Invasive aspergillosis (IA) of central nervous system is a rare but well described disease with a mortality of over 95% in spite of antifungal and surgical therapy. We present a case of cerebral abscess due to *Aspergillus fumigatus*, cured with liposomal amphotericin and surgery.

A 16-year old male with severe medullary aplasia began receiving immunosuppressive treatment according to the protocol of the *German Aplastic Anaemia Study Group.*[1] On day 6 of the treatment he developed a crisis comicial. He was afebrile and physical examination did not reveal any abnormality. NMR scans (Figure 1) showed a mass in the left parietal lobe with zones of subacute bleeding and peripheral edema causing partial collapse of the left ventricle with heterogeneous contrast capture. Chest radiography and lumbar puncture were normal.

As the patient remained asymptomatic and the radiologic image was unspecific, it was decided to await new developments. On day 36, a chest radiograph showed consolidation in the lower left lobe. Physical examination showed right-sided loss of sensation and minimal paresis of the left arm. CT showed growth of the parenchymatous lesion with encapsulation. Bronchoalveolar lavage and cerebral biopsy yielded *A. fumigatus.*

Conventional amphotericin was initiated at a dose of 1 mg/kg/day. Two weeks later, the patient began to develop respiratory symptoms so itraconazole was added at a dose of 600 mg/day. The absence of clinical or radiologic response after 32 days of treatment, together with the development of nephrotoxicity made it necessary to change to a liposomal amphotericin (Ambisome®) at a dosage of 1.5 mg/kg/day.

On day 123, no hematologic response had been produced, so the same immunosuppressive cycle was begun again.

After 20 days of treatment with liposomal amphotericin, the pulmonary infiltration disappeared while the cerebral lesion was unchanged, so surgical excision was carried out. After surgery, liposomal amphotericin was suspended and itraconazole treatment maintained at 800 mg/day.

Two weeks after the operation, bradypsychia was observed and another CT scan (Figure 2) showed relapse of the lesion. At that moment, hematologic response began. After 40 days of treatment, no improvement in the lesion was seen, so another therapeutic change to liposomal amphotericin was made and another excision of the aspergilloma and the infiltrated parietal bone carried out. Liposomal amphotericin was maintained for 350 days (total dose: 35 g) with good tolerance and follow-up maintenance for 12 months with itraconazole at 200 mg/day. Control CT scans show no relapse of the aspergilloma to date. Physical examination is normal, with no neurological deficit.

IA is a common infection in immune-compromised patients. Diagnosis is difficult in the absence of histologic confirmation. The mortality associated with Aspergillus infection in this type of patient is high. In a review by Stevens,[2] only 8 of 33 patients responded to treatment. The most common clinical manifestations are persistent fever in spite of broad-spectrum antibiotic treatment, the appearance of pulmonary infiltration and, at the CNS level, focal neurologic deficits.[3] Recent publications[4] consider the appearance of cerebral infarcts in IA-risk patients, even without lung disease, to be an indication for the start of aggressive antifungal treatment.

The treatment of cerebral aspergillosis has been

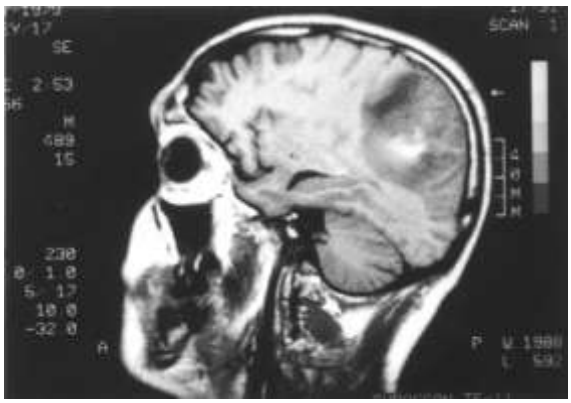

Figure 1.