ABSTRACT

Background. The estimated incidence of acute promyelocytic leukemia (APL) is approximately 6 cases per 10 million people per year with no apparent differences between sexes. The age of APL cases is younger than that of other acute myeloid leukemias (AML). Spatial and temporal clusters of APL have been reported. These observations suggest a possible selective role for environmental and/or occupational factors in APL development.

Methods. A multicenter case-control study was carried out on risk factors for acute leukemias and preleukemias. In this report data related to APL are selectively analyzed from the larger study to identify specific risk factors.

Results. The case-control study on 38 cases of APL showed a strong association with shoemaking (odds ratio 6.3, 95% confidence interval 1.3-31.1). A moderate leukemogenic effect from living in houses built with tuff, a porous building material containing $\gamma$-emitting radionuclides and having a high radon concentration, and from using hair dyes was also suggested.

Conclusions. These data, together with the reported spatial and temporal clustering of APL, support the hypothesis of specific environmental and/or occupational risk factors for APL among other AML subtypes and indicate the need for additional ad hoc multicenter studies.

Key words: leukemia, promyelocytic leukemia, epidemiology, risk factors
described elsewhere in detail. Briefly, cases were at least 15-year-old with newly diagnosed leukemias or pre-leukemias (refractory anemias with excess of blasts, RAEB). Diagnostic criteria were based on the revised French-American-British (FAB) classification of bone marrow aspirates. Controls were recruited in the region of the study hospital during the study period from among outpatients with no hematologic malignancy, and they were seen in the same hospitals in which the cases had been identified.

Controls diagnosed with platelet disorders, leukocytosis, leukopenias or monoclonal gammopathies of undetermined significance were excluded due to possible shared risk factors with the case diseases.

A standard precoded questionnaire was administered to both cases and controls.

In this paper, among all leukemia and pre-leukemia cases we considered only patients with APL observed in the three Hematology Centers and compared them with the same control groups.

Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were computed by unconditional logistic regression. Age, sex, education and residence were considered in the analysis.

Results

Thirty-eight APL cases were observed among 254 AML patients. Center-by-center, APL and AML other than APL were respectively: 15 and 103 in Rome, 8 and 56 in Bologna, 15 and 57 in Pavia. Male:female ratio was 1:1 with 71% of patients between 15 and 54 years of age and 21% younger than 24. Conversely, 52% of the AML cases excluding APL were older than 54 (Table 1).

Two of the 38 APL cases recruited for the case-control study described here had a history of previous cancer: a female with apudoma and breast cancer and a male with cancer of the larynx. Both cases were treated by radiotherapy.

The remaining 36 cases were compared to 1161 controls (399 males and 762 females). Table 1 shows the age distribution of controls. In Table 2 we report the odds ratios of considered risk factors, estimated in the case-control study, after excluding the two cases with a history of cancer.

A highly significant association was found between APL cases and shoemaking (OR 6.3, 95% CI 1.3-31.1), higher than that observed in the other AML varieties (OR 1.9, 95% CI 0.5-7.2). None of the remaining APL cases were employed in other areas of occupational risk considered in the main study, i.e. electrical worker, painter, child-care worker, hairdresser, professional herbicide or pesticide user. A slight association (not statistically significant) was found for living in houses built with tuff (OR 1.3, 95% CI 0.4-4.5) and for using hair dyes (OR 1.5, 95% CI 0.6-3.7). A slight increased odds ratio was shown for frequent hair dye use (at least once every 2 months) and use of dark color hair dyes (Table 2).

Discussion

APL is a very rare condition with an incidence rate of approximately 6 cases for every 10 million people with no differences in sex distribution.

Available data are drawn from reports in the literature with particular emphasis on the study carried out by 20 Italian hematology centers. In the present work APL patients are younger than their other AML counterparts, and a significant number of them are under 24 years of age. This findings may partly explain the rela-
tively good prognosis of this AML subtype.

The minimum annual cumulative incidence rate calculated on the 256 cases of APL collected in Italy between 1980 and 1988 was estimated to be 0.6 per million people per year with no differences between sexes. The highest incidence rate was observed in the 25-54 age group and 80% of cases were in the 15-54 age group.3

Gilbert et al. described a childhood spatial cluster of APL.2 Seven out of nine patients with APL seen from 1981 to 1985 at the Red Cross War Memorial Children’s Hospital of Cape Town (South Africa) were from the Eastern Cape.2 Spatial clustering of APL in children has also been described in Milan, Italy.4

The time distribution of cases collected by the Italian collaborative group showed a slight increase during spring and autumn as compared to winter and summer.3

The reports of temporal and spatial clustering of APL suggest a possible role for seasonal and environmental factors, but additional studies are needed to confirm these hypotheses.

Cuttner reported that 5 out of 16 cases (31%) of APL admitted to the Mount Sinai Hospital from 1974 to 1981 had a history of ulcerative colitis, suggesting a possible relationship between APL and immunosuppressive therapy.1

Two cases in our study had been previously treated with radiotherapy; nevertheless this hypothesis must also be confirmed in larger patient populations.

The Italian case-control study on acute leukemias indicated as possible risk factors dark hair dyes, shoemaking, painting, child-care occupations, electrical work, living in houses built with tuff and smoking.4 Given the small number of APL cases, only a few of these risk factors could be considered in the present report.

The significant relationship between shoemaking and APL is possibly related to benzene exposure, a well-known leukemogenic agent present in the glues.9-11 An excess of M3 (promyelocytic) subtypes was also found among subjects exposed to benzene in a case-control study on occupational risk factors for acute leukemias.12 If these data are confirmed by further studies, the high risk of developing AML after benzene exposition could be largely attributed to the APL subset.

We found a non significant association between APL and tuff and hair dyes use. Tuff is a building material of volcanic origin that contains α-emitting radionuclides and has a high radon concentration; it is used in housing construction particularly in Central and Southern Italy.6 A high radon concentration in houses has
been found to be associated with an elevated frequency of mutations in the peripheral lymphocytes of exposed subjects, making an association between tuff and APL biologically plausible. A cluster of ALL in children has been reported in an area of Southern Italy with a high density of tuff houses, and a mortality study found an increased risk for myeloid leukemia in Viterbo, an area of volcanic origin near Rome.

A recent case-control study found relationships between dark hair dye exposure and Hodgkin’s and non Hodgkin’s lymphomas and myeloma; two previous similar studies indicated an association between these two factors and leukemias. Our findings also suggest a modest leukemogenic effect for hair dye use, though the small number of APL cases recruited in the present case-control study does not provide conclusive evidence for these associations.

Seasonal and spatial clustering of APL indicates the need for additional ad hoc studies to verify whether this disease is linked to spatial or seasonal leukemic factors. Moreover, these studies might also clarify why APL patients are younger than their other AML counterparts.

References